It's a Brave New World:
Science and Technology Collide with Legal Ethics

The G. Thomas VanBebber Fourteenth Annual Ethics in Litigation Forum
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Presented by the Earl E. O'Connor Inn of Court

It's a Brave New World

Science and Technology Collide with Legal Ethics

Biographies of Speakers

Professor Gary Marchant

Gary Marchant is the Lincoln Professor Emerging Technologies, Law and Ethics at the Sandra Day O'Connor College of Law at Arizona State University. He is also a Professor of Life Sciences at ASU and Executive Director of the ASU Center for the Study of Law, Science and Technology. Professor Marchant has a Ph.D. in Genetics from the University of British Columbia, a Masters of Public Policy degree from the Kennedy School of Government, and a law degree from Harvard. Prior to joining the ASU faculty in 1999, he was a partner in a Washington, D.C. law firm where his practice focused on environmental and administrative law. Professor Marchant teaches and researches in the subject areas of environmental law, risk assessment and risk management, genetics and the law, biotechnology law, food and drug law, legal aspects of nanotechnology, and law, science and technology.

Shazzie Naseem

Shazzie Naseem, Partner with Berkowitz Oliver LLP, concentrates his practice in the areas of complex federal white collar criminal defense and general business litigation. Prior to joining Berkowitz Oliver in 2006, Shazzie served on active duty for six years as a Lieutenant in the United States Navy's Judge Advocate General's Corps (JAG Corps). In 2004, Shazzie was selected by his Command to act as a Special Assistant United States Attorney in the Central District of California for Naval Base Ventura County where he prosecuted violations of both federal and state law. Shazzie serves as a Criminal Justice Act (CJA) Panel Attorney for the United States District Court for the District of Kansas. Additionally, he travels the country as a faculty member for the Administrative Office of the United States District Courts Office of Defender Services Training Branch Law and Technology Series, which trains lawyers and paralegals on the successful use and implementation of technology in the practice of law. Shazzie received his undergraduate degree in Philosophy and Religion from Truman State University in 1997 and graduated from The University of Notre Dame Law School in 2000.

Dean Ellen Suni

Ellen Yankiver Suni, Dean and Professor of Law, UMKC School of Law, has taught Professional Responsibility for over thirty years. She has served on various state and national committees in this area and has served as a consultant to the Missouri Supreme Court Advisory Committee and the Office of Chief Disciplinary Counsel. She has authored articles in the area, done consulting and training and served as an expert witness. She is a regular speaker on topics related to lawyer ethics and professional responsibility and has been speaking on legal ethics as it relates to technology since the early 1990's.

Biographies of Speakers *Continued*

Judge David Waxse

District of Kansas Magistrate Judge David J. Waxse earned his B.A. degree from the University of Kansas and his juris doctorate degree from Columbia University. Prior to his appointment as a Magistrate Judge in 1999, he was a partner at Shook, Hardy & Bacon. From 1992-1999, Judge Waxse was a member, and one time chair, of the Kansas Commission on Judicial Qualifications, the state judicial discipline

organization. He was also a member of the Civil Justice Reform Act Advisory Committee and the Mediation Panel for the United States District Court for the District of Kansas. In addition, he served on the Kansas Justice Commission, established by the Kansas Supreme Court to implement the Citizens' Justice Initiative review of the state justice system. Judge Waxse is a Past-President of the Kansas Bar Association and, as a KBA delegate to the American Bar Association House of Delegates, was a member of the Board of Governors of the KBA for twelve years. He is vice chair of the Judicial Division of the ABA and a member of the Judicial Division's Ethics Committee. He has been a lecturer in law at the University of Kansas School of Law and has made presentations on e-discovery nationally and internationally.

Jennifer Haaga

Jennifer L. Haaga joined the KU Center for Technology Commercialization as Assistant Director of Industry Agreements in October 2012. She is responsible for negotiating and drafting agreements including CDAs, MTAs, Sponsored Research Agreements and Service Agreements in all areas of technology with industry partners. Before joining KUCTC, Jennifer served for two years as a research attorney for the Hon. G. Gordon Atcheson on the Kansas Court of Appeals. During her time as a law student, she was an extern at KUCTC and worked as a research assistant for Prof. Hoeflich and KU General Counsel's office. Jennifer graduated from the University of Kansas Law School in 2010 and also has undergraduate degrees from KU in Organismal Biology and Psychology.

Kansas Rules of Professional Conduct

1.1 - Client-Lawyer Relationship: Competence

A lawyer shall provide competent representation to a client. Competent representation requires the legal knowledge, skill, thoroughness and preparation reasonably necessary for the representation.

Comment:

Legal Knowledge and Skill

[1] In determining whether a lawyer employs the requisite knowledge and skill in a particular matter, relevant factors include the relative complexity and specialized nature of the matter, the lawyer's general experience, the lawyer's training and experience in the field in question, the preparation and study the lawyer is able to give the matter and whether it is feasible to refer the matter to, or associate or consult with, a lawyer of established competence in the field in question. In many instances, the required proficiency is that of a general practitioner. Expertise in a particular field of law may be required in some circumstances.

[2] A lawyer need not necessarily have special training or prior experience to handle legal problems of a type with which the lawyer is unfamiliar. A newly admitted lawyer can be as competent as a practitioner with long experience. Some important legal skills, such as the analysis of precedent, the evaluation of evidence and legal drafting, are required in all legal problems. Perhaps the most fundamental legal skill consists of determining what kind of legal problems a situation may involve, a skill that necessarily transcends any particular specialized knowledge. A lawyer can provide adequate representation in a wholly novel field through necessary study. Competent representation can also be provided through the association of a lawyer of established competence in the field in question.

[3] In an emergency a lawyer may give advice or assistance in a matter in which the lawyer does not have the skill ordinarily required where referral to or consultation or association with another lawyer would be impractical. Even in an emergency, however, assistance should be limited to that reasonably necessary in the circumstances, for ill considered action under emergency conditions can jeopardize the client's interest.

[4] A lawyer may accept representation where the requisite level of competence can be achieved by reasonable preparation. This applies as well to a lawyer who is appointed as counsel for an unrepresented person. See also Rule 6.2.

Kansas Rules of Professional Conduct *Continued*

Thoroughness and Preparation

[5] Competent handling of a particular matter includes inquiry into and analysis of the factual and legal elements of the problem, and use of methods and procedures meeting the standards of competent practitioners. It also includes adequate preparation. The required attention and preparation are determined in part by what is at stake; major litigation and complex transactions ordinarily require more elaborate treatment than matters of lesser consequence.

Maintaining Competence

[6] To maintain the requisite knowledge and skill, a lawyer should engage in continuing study and education. If a system of peer review has been established, the lawyer should consider making use of it in appropriate circumstances.

1.2 - Scope of Representation

(a) A lawyer shall abide by a client's decisions concerning the lawful objectives of representation, subject to paragraphs (c), (d), and (e), and shall consult with the client as to the means which the lawyer shall choose to pursue. A lawyer shall abide by a client's decision whether to settle a matter. In a criminal case, the lawyer shall abide by the client's decision, after consultation with the lawyer, as to a plea to be entered, whether to waive jury trial and whether the client will testify.

(b) A lawyer's representation of a client, including representation by appointment, does not constitute an endorsement of the client's political, economic, social or moral views or activities.

(c) A lawyer may limit the scope of the representation if the limitation is reasonable under the circumstances and the client gives informed consent in writing.

(d) A lawyer shall not counsel a client to engage, or assist a client, in conduct that the lawyer knows is criminal or fraudulent, but a lawyer may discuss the legal consequences of any proposed course of conduct with a client and may counsel or assist a client to make a good faith effort to determine the validity, scope, meaning or application of the law.

(e) When a lawyer knows that a client expects assistance not permitted by the rules of professional conduct or other law, the lawyer shall consult with the client regarding the relevant limitations on the lawyer's conduct.

Kansas Rules of Professional Conduct *Continued*

1.3 - Client-Lawyer Relationship: Diligence

A lawyer shall act with reasonable diligence and promptness in representing a client.

Comment:

[1] A lawyer should pursue a matter on behalf of a client despite opposition, obstruction or personal inconvenience to the lawyer, and may take whatever lawful and ethical measures are required to vindicate a client's cause or endeavor. A lawyer should act with commitment and dedication to the interests of the client and with zeal in advocacy upon the client's behalf. However, a lawyer is not bound to press for every advantage that might be realized for a client. A lawyer has professional discretion in determining the means by which a matter should be pursued. See Rule 1.2. A lawyer's workload should be controlled so that each matter can be handled adequately.

[2] Perhaps no professional shortcoming is more widely resented than procrastination. A client's interests often can be adversely affected by the passage of time or the change of conditions; in extreme instances, as when a lawyer overlooks a statute of limitations, the client's legal position may be destroyed. Even when the client's interests are not affected in substance, however, unreasonable delay can cause a client needless anxiety and undermine confidence in the lawyer's trustworthiness.

[3] Unless the relationship is terminated as provided in Rule 1.16, a lawyer should carry through to conclusion all matters undertaken for a client. If a lawyer's employment is limited to a specific matter, the relationship terminates when the matter has been resolved. If a lawyer has served a client over a substantial period in a variety of matters, the client sometimes may assume that the lawyer will continue to serve on a continuing basis unless the lawyer gives notice of withdrawal. Doubt about whether a client-lawyer relationship still exists should be clarified by the lawyer, preferably in writing, so that the client will not mistakenly suppose the lawyer is looking after the client's affairs when the lawyer has ceased to do so. For example, if a lawyer has handled a judicial or administrative proceeding that produced a result adverse to the client but has not been specifically instructed concerning pursuit of an appeal, the lawyer should advise the client of the possibility of appeal before relinquishing responsibility for the matter.

1.4 - Client-Lawyer Relationship: Communication

(a) A lawyer shall keep a client reasonably informed about the status of a matter and promptly comply with reasonable requests for information.

(b) A lawyer shall explain a matter to the extent reasonably necessary to permit the client to make informed decisions regarding the representation.

Kansas Rules of Professional Conduct *Continued*

Comment:

[1] The client should have sufficient information to participate intelligently in decisions concerning the objectives of the representation and the means by which they are to be pursued, to the extent the client is willing and able to do so. For example, a lawyer negotiating on behalf of a client should provide the client with facts relevant to the matter, inform the client of communications from another party and take other reasonable steps that permit the client to make a decision regarding a serious offer from another party. A lawyer who receives from opposing counsel an offer of settlement in a civil controversy or a proffered plea bargain in a criminal case should promptly inform the client of its substance unless prior discussions with the client have left it clear that the proposal will be unacceptable. See Rule 1.2(a). Even when a client delegates authority to the lawyer, the client should be kept advised of the status of the matter.

[2] Adequacy of communication depends in part on the kind of advice or assistance involved. For example, in negotiations where there is time to explain a proposal, the lawyer should review all important provisions with the client before proceeding to an agreement. In litigation a lawyer should explain the general strategy and prospects of success and ordinarily should consult the client on tactics that might injure or coerce others. On the other hand, a lawyer ordinarily cannot be expected to describe trial or negotiation strategy in detail. The guiding principle is that the lawyer should fulfill reasonable client expectations for information consistent with the duty to act in the client's best interests, and the client's overall requirements as to the character of representation.

[3] Ordinarily, the information to be provided is that appropriate for a client who is a comprehending and responsible adult. However, fully informing the client according to this standard may be impracticable, for example, where the client is a child or suffers from diminished capacity. See Rule 1.14. When the client is an organization or group, it is often impossible or inappropriate to inform every one of its members about its legal affairs; ordinarily, the lawyer should address communications to the appropriate officials of the organization. See Rule 1.13. Where many routine matters are involved, a system of limited or occasional reporting may be arranged with the client. Practical exigency may also require a lawyer to act for a client without prior consultation.

Withholding Information

[4] In some circumstances, a lawyer may be justified in delaying transmission of information when the client would be likely to react imprudently to an immediate communication. Thus, a lawyer might withhold a psychiatric diagnosis of a client when the examining psychiatrist indicates that disclosure would harm the client. A lawyer may not withhold information to serve the lawyer's

Kansas Rules of Professional Conduct *Continued*

own interest or convenience. Rules or court orders governing litigation may provide that information supplied to a lawyer may not be disclosed to the client. Rule 3.4(c) directs compliance with such rules or orders.

1.13 - Client-Lawyer Relationship: Organization as Client

(a) A lawyer employed or retained by an organization represents the organization acting through its duly authorized constituents.

(b) If a lawyer for an organization knows that an officer, employee or other person associated with the organization is engaged in action, intends to act or refuses to act in a matter related to the representation that is a violation of a legal obligation to the organization, or a violation of law which reasonably might be imputed to the organization, and is likely to result in substantial injury to the organization, the lawyer shall proceed as is reasonably necessary in the best interest of the organization. In determining how to proceed, the lawyer shall give due consideration to the seriousness of the violation and its consequences, the scope and nature of the lawyer's representation, the responsibility in the organization and the apparent motivation of the person involved, the policies of the organization concerning such matters and any other relevant considerations. Any measures taken shall be designed to minimize disruption of the organization and the risk of revealing information relating to the representation to persons outside the organization. Such measures may include among others:

(1) asking for reconsideration of the matter;

(2) advising that a separate legal opinion on the matter be sought for presentation to appropriate authority in the organization; and

(3) referring the matter to higher authority in the organization, including, if warranted by the seriousness of the matter, referral to the highest authority that can act in behalf of the organization as determined by applicable law.

(c) If, despite the lawyer's efforts in accordance with paragraph (b), the highest authority that can act on behalf of the organization insists upon action, or a refusal to act, that is clearly a violation of law and is likely to result in substantial injury to the organization, the lawyer shall follow Rule 1.16.

(d) In dealing with an organization's directors, officers, employees, members, shareholders or other constituents, a lawyer shall explain the identity of the client when it is apparent that the organization's interests are adverse to those of the constituents with whom the lawyer is dealing.

Kansas Rules of Professional Conduct *Continued*

(e) A lawyer representing an organization may also represent any of its directors, officers, employees, members, shareholders or other constituents, subject to the provisions of Rule 1.7. If the organization's consent to the dual representation is required by Rule 1.7, the consent shall be given by an appropriate official of the organization other than the individual who is to be represented, or by the shareholders.

Comment:

The Entity as the Client

[1] An organizational client is a legal entity, but it cannot act except through its officers, directors, employees, shareholders and other constituents.

[2] Officers, directors, employees and shareholders are the constituents of the corporate organizational client. The duties defined in this Comment apply equally to unincorporated associations. "Other constituents" as used in this Comment means the positions equivalent to officers, directors, employees and shareholders held by persons acting for organizational clients that are not corporations.

[3] When one of the constituents of an organizational client communicates with the organization's lawyer in that person's organizational capacity, the communication is protected by Rule 1.6. Thus, by way of example, if an organizational client requests its lawyer to investigate allegations of wrong-doing, interviews made in the course of that investigation between the lawyer and the client's employees or other constituents are covered by Rule 1.6. This does not mean, however, the constituents of an organizational client are the clients of the lawyer. The lawyer may not disclose to such constituents information relating to the representation except for disclosures explicitly or impliedly authorized by the organizational client in order to carry out the representation or as otherwise permitted by Rule 1.6.

[4] When constituents of the organization make decisions for it, the decisions ordinarily must be accepted by the lawyer even if their utility or prudence is doubtful. Decisions concerning policy and operations, including ones entailing serious risk, are not as such in the lawyer's province. However, different considerations arise when the lawyer knows that the organization may be substantially injured by action of a constituent that is in violation of law. In such a circumstance, it may be reasonably necessary for the lawyer to ask the constituent to reconsider the matter. If that fails, or if the matter is of sufficient seriousness and importance to the organization, it may be reasonably necessary for the lawyer to take steps to have the matter reviewed by a higher authority in the organization. Clear justification should exist for seeking review over the head of the constituent normally responsible for it. The stated policy of the organization may define circumstances and prescribe channels for such review, and a lawyer should encourage the formulation of such a policy. Even in the absence of organization policy, however, the lawyer

Kansas Rules of Professional Conduct *Continued*

may have an obligation to refer a matter to higher authority, depending on the seriousness of the matter and whether the constituent in question has apparent motives to act at variance with the organization's interest. Review by the chief executive officer or by the board of directors may be required when the matter is of importance commensurate with their authority. At some point it may be useful or essential to obtain an independent legal opinion.

[5] In an extreme case, it may be reasonably necessary for the lawyer to refer the matter to the organization's highest authority. Ordinarily, that is the board of directors or similar governing body. However, applicable law may prescribe that under certain conditions highest authority reposes elsewhere; for example, in the independent directors of a corporation.

Relation to Other Rules

[6] The authority and responsibility provided in paragraph (b) are concurrent with the authority and responsibility provided in other Rules. In particular, this Rule does not limit or expand the lawyer's responsibility under Rules 1.6, 1.8, and 1.16, 3.3 or 4.1. If the lawyer's services are being used by an organization to further a crime or fraud by the organization, Rule 1.2(d) can be applicable.

Government Agency

[7] The duty defined in this Rule applies to governmental organizations. However, when the client is a governmental organization, a different balance may be appropriate between maintaining confidentiality and assuring that the wrongful official act is prevented or rectified, for public business is involved. In addition, duties of lawyers employed by the government or lawyers in military service may be defined by statutes and regulation. Therefore, defining precisely the identity of the client and prescribing the resulting obligations of such lawyers may be more difficult in the government context. Although in some circumstances the client may be a specific agency, it is generally the government as a whole. For example, if the action or failure to act involves the head of a bureau, either the department of which the bureau is a part or the government as a whole may be the client for purpose of this Rule. Moreover, in a matter involving the conduct of government officials, a government lawyer may have authority to question such conduct more extensively than that of a lawyer for a private organization in similar circumstances. This Rule does not limit that authority. See note on Scope.

Clarifying the Lawyer's Role

[8] There are times when the organization's interest may be or become adverse to those of one or more of its constituents. In such circumstances the lawyer should advise any constituent, whose interest the lawyer finds adverse to that of the organization of the conflict or potential conflict of interest, that the lawyer cannot represent such constituent, and that such person may wish to

Kansas Rules of Professional Conduct *Continued*

obtain independent representation. Care must be taken to assure that the individual understands that, when there is such adversity or interest, the lawyer for the organization cannot provide legal representation for that constituent individual, and that discussions between the lawyer for the organization and the individual may not be privileged.

[9] Whether such a warning should be given by the lawyer for the organization to any constituent individual may turn on the facts of each case.

Dual Representation

[10] Paragraph (e) recognizes that a lawyer for an organization may also represent a principal officer or major shareholder.

Derivative Actions

[11] Under generally prevailing law, the shareholders or members of a corporation may bring suit to compel the directors to perform their legal obligations in the supervision of the organization. Members of unincorporated associations have essentially the same right. Such an action may be brought nominally by the organization, but usually is, in fact, a legal controversy over management of the organization.

[12] The question can arise whether counsel for the organization may defend such an action. The proposition that the organization is the lawyer's client does not alone resolve the issue. Most derivative actions are a normal incident of an organization's affairs, to be defended by the organization's lawyer like any other suit. However, if the claim involves serious charges of wrongdoing by those in control of the organization, a conflict may arise between the lawyer's duty to the organization and the lawyer's relationship with the board. In those circumstances, Rule 1.7 governs who should represent the directors and the organization.

1.16 - <u>Client-Lawyer Relationship: Declining or Terminating Representation</u>

(a) Except as stated in paragraph (c), a lawyer shall not represent a client or, where representation has commenced, shall withdraw from the representation of a client if:

(1) the representation will result in violation of the rules of professional conduct or other law;

(2) the lawyer's physical or mental condition materially impairs the lawyer's ability to represent the client;

(3) the lawyer is discharged; or

Kansas Rules of Professional Conduct *Continued*

(4) the client persists in a course of action involving the lawyer's services that the lawyer reasonably believes is criminal or fraudulent.

(b) Except as stated in paragraph (c), a lawyer may withdraw from representing a client if withdrawal can be accomplished without material adverse effect on the interests of the client, or if:

(1) the client has used the lawyer's services to perpetrate a crime or fraud;

(2) a client insists upon pursuing an objective that the lawyer considers repugnant or imprudent;

(3) the client fails substantially to fulfill an obligation to the lawyer regarding the lawyer's services and has been given reasonable warning that the lawyer will withdraw unless the obligation is fulfilled;

(4) the representation will result in an unreasonable financial burden on the lawyer or has been rendered unreasonably difficult by the client; or

(5) other good cause for withdrawal exists.

(c) When ordered to do so by a tribunal, a lawyer shall continue representation notwithstanding good cause for terminating the representation.

(d) Upon termination of representation, a lawyer shall take steps to the extent reasonably practicable to protect a client's interests, such as giving reasonable notice to the client, allowing time for employment of other counsel, surrendering papers and property to which the client is entitled and refunding any advance payment of fee that has not been earned. The lawyer may retain papers relating to the client to the extent permitted by other law.

Comment:

[1] A lawyer should not accept representation in a matter unless it can be performed competently, promptly, without improper conflict of interest and to completion.

Mandatory Withdrawal

[2] A lawyer ordinarily must decline or withdraw from representation if the client demands that the lawyer engage in conduct that is illegal or violates the Rules of Professional Conduct or other law. The lawyer is not obliged to decline or withdraw simply because the client suggests such a

Kansas Rules of Professional Conduct *Continued*

course of conduct; a client may make such a suggestion in the hope that a lawyer will not be constrained by a professional obligation.

[3] When a lawyer has been appointed to represent a client, withdrawal ordinarily requires approval of the appointing authority. See also Rule 6.2. Difficulty may be encountered if withdrawal is based on the client's demand that the lawyer engage in unprofessional conduct. The court may wish an explanation for the withdrawal, while the lawyer may be bound to keep confidential the facts that would constitute such an explanation. The lawyer's statement that professional considerations require termination of the representation ordinarily should be accepted as sufficient.

Discharge

[4] A client has a right to discharge a lawyer at any time, with or without cause, subject to liability for payment for the lawyer's services. Where future dispute about the withdrawal may be anticipated, it may be advisable to prepare a written statement reciting the circumstances.

[5] Whether a client can discharge appointed counsel may depend on applicable law. A client seeking to do so should be given a full explanation of the consequences. These consequences may include a decision by the appointing authority that appointment of successor counsel is unjustified, thus requiring the client to represent himself or herself.

[6] If the client is mentally incompetent, the client may lack the legal capacity to discharge the lawyer, and in any event the discharge may be seriously adverse to the client's interests. The lawyer should make special effort to help the client consider the consequences and, in an extreme case, may initiate proceedings for a conservatorship or similar protection of the client. See Rule 1.14.

Optional Withdrawal

[7] A lawyer may withdraw from representation in some circumstances. The lawyer has the option to withdraw if it can be accomplished without material adverse effect on the client's interests. Withdrawal is required if the client persists in a course of action that the lawyer reasonably believes is criminal or fraudulent, for a lawyer should not be associated with such conduct even if the lawyer does not further it. Withdrawal is permitted if the lawyer's services were misused in the past even if that would materially prejudice the client. The lawyer also may withdraw where the client insists on a repugnant or imprudent objective.

[8] A lawyer may withdraw if the client refuses to abide by the terms of an agreement relating to the representation, such as an agreement concerning fees or court costs or an agreement limiting the objectives of the representation.

Kansas Rules of Professional Conduct *Continued*

Assisting the Client Upon Withdrawal

[9] Even if the lawyer has been unfairly discharged by the client, a lawyer must take all reasonable steps to mitigate the consequences to the client. The lawyer may retain papers as security for a fee only to the extent permitted by law.

[10] Whether or not a lawyer for an organization may under certain unusual circumstances have a legal obligation to the organization after withdrawing or being discharged by the organization's highest authority is beyond the scope of these Rules.

3.8 - Advocate: Special Responsibilities of a Prosecutor

The prosecutor in a criminal case shall:

(a) refrain from prosecuting a charge that the prosecutor knows is not supported by probable cause;

(b) make reasonable efforts to assure that the accused has been advised of the right to, and the procedure for obtaining, counsel and has been given reasonable opportunity to obtain counsel;

(c) not seek to obtain from an unrepresented accused a waiver of important pretrial rights, such as the right to a preliminary hearing;

(d) make timely disclosure to the defense of all evidence or information known to the prosecutor that tends to negate the guilt of the accused or mitigates the offense, and, in connection with sentencing, disclose to the defense and to the tribunal all unprivileged mitigating information known to the prosecutor, except when the prosecutor is relieved of this responsibility by a protective order of the tribunal; and

(e) not subpoena a lawyer in a grand jury or other criminal proceeding to present evidence about a past or present client unless the prosecutor reasonably believes:

(1) the information sought is not protected from disclosure by any applicable privilege;

(2) the evidence sought is essential to the successful completion of an ongoing investigation or prosecution; and

(3) there is no other feasible alternative to obtain the information;

(f) except for statements that are necessary to inform the public of the nature and extent of the prosecutor's action and that serve a legitimate law enforcement purpose, refrain from making

Kansas Rules of Professional Conduct *Continued*

extrajudicial comments that have a substantial likelihood of heightening public condemnation of the accused and exercise reasonable care to prevent investigators, law enforcement personnel, employees or other persons assisting or associated with the prosecutor in a criminal case from making an extrajudicial statement that the prosecutor would be prohibited from making under Rule 3.6 or this Rule.

Comment:

[1] A prosecutor has the responsibility of a minister of justice and not simply that of an advocate. This responsibility carries with it specific obligations to see that the defendant is accorded procedural justice and that guilt is decided upon the basis of sufficient evidence. Precisely how far the prosecutor is required to go in this direction is a matter of debate and varies in different jurisdictions. Many jurisdictions have adopted the ABA Standards of Criminal Justice Relating to Prosecution Function, which in turn are the product of prolonged and careful deliberation by lawyers experienced in both criminal prosecution and defense. Applicable law may require other measures by the prosecutor and knowing disregard of those obligations or a systematic abuse of prosecutorial discretion could constitute a violation of Rule 8.4.

[2] In some jurisdictions, a defendant may waive a preliminary hearing and thereby lose a valuable opportunity to challenge probable cause. Accordingly, prosecutors should not seek to obtain waivers of preliminary hearings or other important pretrial rights from unrepresented accused persons. Paragraph (c) does not apply, however, to an accused appearing pro se with the approval of the tribunal. Nor does it forbid the lawful questioning of an uncharged suspect who has knowingly waived the rights to counsel and silence.

[3] The exception in paragraph (d) recognizes that a prosecutor may seek an appropriate protective order from the tribunal if disclosure of information to the defense could result in substantial harm to an individual or to the public interest.

[4] Paragraph (e) is intended to limit the issuance of lawyer subpoenas in grand jury and other criminal proceedings to those situations in which there is a genuine need to intrude into the client-lawyer relationship.

[5] Paragraph (f) supplements Rule 3.6, which prohibits extrajudicial statements that have a substantial likelihood of prejudicing an adjudicatory proceeding. In the context of a criminal prosecution, a prosecutor's extrajudicial statement can create the additional problem of increasing public condemnation of the accused. Although the announcement of an indictment, for example, will necessarily have severe consequences for the accused, a prosecutor can, and should, avoid comments which have no legitimate law enforcement purpose and have a substantial likelihood of increasing public opprobrium of the accused. Nothing in this Comment

Kansas Rules of Professional Conduct *Continued*

is intended to restrict the statements which a prosecutor may make which comply with Rule 3.6(b) or 3.6(c).

[6] Like other lawyers, prosecutors are subject to Rules 5.1 and 5.3, which relate to responsibilities regarding lawyers and nonlawyers who work for or are associated with the lawyer's office. Paragraph (f) reminds the prosecutor of the importance of these obligations in connection with the unique dangers of improper extrajudicial statements in a criminal case. In addition, paragraph (f) requires a prosecutor to exercise reasonable care to prevent persons assisting or associated with the prosecutor from making improper extrajudicial statements, even when such persons are not under the direct supervision of the prosecutor. Ordinarily, the reasonable care standard will be satisfied if the prosecutor issues the appropriate cautions to law-enforcement personnel and other relevant individuals.

4.4 - Transactions with Persons other than Clients: Respect for Rights of Third Persons

(a) In representing a client, a lawyer shall not use means that have no substantial purpose other than to embarrass, delay, or burden a third person, or use methods of obtaining evidence that violate the legal rights of such a person.

(b) A lawyer who receives a document relating to the representation of the lawyer's client and knows or reasonably should know that the document was inadvertently sent shall promptly notify the sender.

Comment:

[1] Responsibility to a client requires a lawyer to subordinate the interests of others to those of the client, but that responsibility does not imply that a lawyer may disregard the rights of third persons. It is impractical to catalog all such rights, but they include legal restrictions on methods of obtaining evidence from third persons and unwarranted intrusion into privileged relationships, such as the client-lawyer relationship.

[2] Paragraph (b) recognizes that lawyers sometimes receive documents that were mistakenly sent or produced by opposing parties or their lawyers. If a lawyer knows or reasonably should know that such a document was sent inadvertently, then this Rule requires the lawyer to promptly notify the sender in order to permit that person to take protective measures. Whether the lawyer is required to take additional steps, such as returning the original document, is a matter of law beyond the scope of these Rules, as is the question of whether the privileged status of a document has been waived. Similarly, this Rule does not address the legal duties of a lawyer who receives a document that the lawyer knows or reasonably should know may have been

Kansas Rules of Professional Conduct *Continued*

wrongfully obtained by the sending person. For purposes of this Rule, "document" includes e-mail or other electronic modes of transmission subject to being read or put into readable form.

[3] Some lawyers may choose to return a document unread, for example, when the lawyer learns before receiving the document that it was inadvertently sent to the wrong address. Where a lawyer is not required by applicable law to do so, the decision to voluntarily return such a document is a matter of professional judgment ordinarily reserved to the lawyer. See Rules 1.2 and 1.4.

8.4 - Maintaining the Integrity of the Profession: Misconduct

It is professional misconduct for a lawyer to:

(a) Violate or attempt to violate the rules of professional conduct, knowingly assist or induce another to do so, or do so through the acts of another;

(b) commit a criminal act that reflects adversely on the lawyer's honesty, trustworthiness or fitness as a lawyer in other respects;

(c) engage in conduct involving dishonesty, fraud, deceit or misrepresentation;

(d) engage in conduct that is prejudicial to the administration of justice;

(e) state or imply an ability to influence improperly a government agency or official;

(f) knowingly assist a judge or judicial officer in conduct that is a violation of applicable rules of judicial conduct or other law; or

(g) engage in any other conduct that adversely reflects on the lawyer's fitness to practice law.

Comment:

[1] Lawyers are subject to discipline when they violate or attempt to violate the Rules of Professional Conduct, knowingly assist or induce another to do so or do so through the acts of another, as when they request or instruct an agent to do so on the lawyer's behalf. Paragraph (a), however, does not prohibit a lawyer from advising a client concerning action the client is legally entitled to take.

[2] Many kinds of illegal conduct reflect adversely on fitness to practice law, such as offenses involving fraud and the offense of willful failure to file an income tax return. However, some kinds of offense carry no such implication. Traditionally, the distinction was drawn in terms of

Kansas Rules of Professional Conduct *Continued*

offenses involving "moral turpitude." That concept can be construed to include offenses concerning some matters of personal morality, such as adultery and comparable offenses, that have no specific connection to fitness for the practice of law. Although a lawyer is personally answerable to the entire criminal law, a lawyer should be professionally answerable only for offenses that indicate lack of those characteristics relevant to law practice. Offenses involving violence, dishonesty, or breach of trust, or serious interference with the administration of justice are in that category. A pattern of repeated offenses, even ones of minor significance when considered separately, can indicate indifference to legal obligation.

[3] A lawyer may refuse to comply with an obligation imposed by law upon a good faith belief that no valid obligation exists. The provisions of Rule 1.2(d) concerning a good faith challenge to the validity, scope, meaning or application of the law apply to challenges of legal regulation of the practice of law.

[4] Lawyers holding public office assume legal responsibilities going beyond those of other citizens. A lawyer's abuse of public office can suggest an inability to fulfill the professional role of attorney. The same is true of abuse of positions of private trust such as trustee, executor, administrator, guardian, agent and officer, director or manager of a corporation or other organization.

What Does the History of Technology Regulation Teach Us about Nano Oversight?

Gary E. Marchant, Douglas J. Sylvester, and Kenneth W. Abbott

"We live in reference to past experience and not to future events, however inevitable."

— H. G. Wells[1]

Nanotechnology is the latest in a growing list of emerging technologies that includes nuclear technologies, genetics, reproductive biology, biotechnology, information technology, robotics, communication technologies, surveillance technologies, synthetic biology, and neuroscience. As was the case for many of the technologies that came before, a key question facing nanotechnology is what type of regulatory oversight is appropriate for this emerging technology. As two of us wrote several years ago, the question facing nanotechnology is not whether it will be regulated, but when and how.[2]

Yet, appropriate regulation of nanotechnology will be challenging. The term "nanotechnology" incorporates a broad, diverse range of materials, technologies, and products, with an even greater spectrum of potential risks and benefits. This technology slashes across the jurisdiction of many existing regulatory statutes and regulatory agencies, and does so across the globe. Nanotechnology is developing at an enormously rapid rate, perhaps surpassing the capability of any potential regulatory framework to keep pace. Finally, the risks of nanotechnology remain largely unknown, both because of the multitude of variations in the technology and because of the limited applicability of traditional toxicological approaches such as structure-activity relationship (SAR) to nanotechnology products.[3]

In the face of these challenges, legislators, regulators, industry officials, non-governmental organizations (NGOs), and academics are all struggling to find a workable regulatory path for oversight of nanotechnology. In crafting such a strategy, there is much we can learn from previous attempts to regulate other emerging technologies. While there are no doubt numerous possible lessons that can be drawn from the history of

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technology regulation, we suggest that the following five lessons should be given strong consideration in designing oversight frameworks for nanotechnology.

Lesson 1: Central Importance of Public Confidence/Trust

The most obvious and widely accepted lesson from the history of technology regulation is the critical role of public confidence and trust. While scientific risk assessment and economic calculations are part of sound regulatory decision making, they alone cannot assure a viable regulatory scheme in the absence of public trust. Time after time, we have seen examples in which a single incident gone awry undermined years of careful planning and building of regulatory systems. Examples include the Three Mile Island nuclear accident,[4] the contamination of the food supply with genetically modified "Starlink" corn that had been approved only for use in animal feed,[5] and the tragic death of Jesse Gelsinger in a gene therapy clinical trial.[6] All of these incidents sparked subsequent official investigations and media scrutiny that revealed significant flaws and failures in the regulatory system that severely undermined public trust in both the technology at issue, and the regulatory programs responsible for the oversight of that technology.

False assurances of safety can also undermine trust in regulators and regulatory systems. A classic example of this effect is the British Government's assurance in the late 1980s and early 1990s that the "mad cow" disease affecting British cattle had no probability of spreading to humans. When British citizens soon began falling ill and dying from the human version of "mad cow" disease (Creutzfeldt-Jakob disease, or CJD), the credibility of British regulators suffered long-term damage.[7]

Public trust is much easier lost than earned, and once lost, it is very difficult to restore.[8] Surveys indicate that public trust in nanotechnology and its oversight requires an active and formal governmental regulatory role.[9] Accordingly, it seems that the establishment of a regulatory scheme is a prerequisite for maintaining public trust, providing another rationale for adoption of regulation beyond the substantive need for such provisions.[10]

Lesson 2: Level the Playing Field

Perhaps in tension with the first lesson on the need to impose regulatory oversight that will promote public confidence, the second lesson from past efforts is to avoid the temptation to impose discriminatory regulatory burdens on new technologies, even when public sentiment seems to weigh in favor of such restrictions. New technologies and products often have lower risks than the technologies and products they are intended to replace, yet are often subject to stigmatization by the media and advocacy groups resulting in more stringent regulation.[11] At the same time, powerful new technologies such as nanotechnology will undoubtedly impose real risks in at least some applications or contexts. In seeking to predict and prevent such risks, regulation must take care not to selectively target products made using a particular process or technology in the absence of evidence showing that the process or technology is any riskier than alternatives.

The European Union (EU) has violated this principle by regulating food made using genetic engineering much more stringently than equivalent products made using other methods. All foods containing genetically modified (GM) ingredients are per se subject to stringent and burdensome authorization, labeling, and traceability requirements that do not apply to non-GM foods.[12] Scientific authorities around the world have consistently concluded that GM foods as a category are no riskier than any other type of food.[13] In fact, the EU's own scientific advisors concluded that "[t]he use of more precise technology and the greater regulatory scrutiny probably make (GM products) even safer than conventional plants and foods."[14]

Notwithstanding this scientific opinion, GM foods are regulated more stringently than other foods in the EU, and to a lesser extent also in the United States. Not only is this discrimination contrary to prevailing scientific opinion, it is also irrational. Consider the

At the very time that technology is accelerating, both legislative and regulatory decision-making institutions seem to be bogging down and becoming slower. Congress is handcuffed by the synergistic effect of an impossibly large number of important issues needing attention mixed with partisan gridlock, making prompt action on any but the most urgent or symbolic issues unlikely.

example of herbicide-resistant crops.[15] Some herbicide-resistant crops have been produced using genetic engineering, but some cultivars with the same trait have also been produced using other means, including chemical or nuclear mutagenesis. These latter techniques are much less precise than genetic engineering, and are likely to generate numerous other mutations along the genome in addition to the herbicide-resistance trait of interest.[16] The National Academy of Sciences has noted that "a mutation made by traditional techniques may be accompanied by many unknown mutations, which often have deleterious effects on the organism."[17] Yet, in "what can only be described as a culture of irrationality," the regulatory structure penalizes the arguably safer GM crop by regulating it, but not the mutation-laden crop expressing the same trait produced by other methods.[18]

Proposals for *sui generis* regulation of nanotechnology products create a similar risk of irrational discrimination. If we have two products with the same functionality — one produced using nanotechnology and the other not — it is not certain or obvious that the nanotechnology version will necessarily be the riskier of the two. They may have the same risks or in some cases the nanotechnology product might even be safer. Automatically treating nanotechnology as more dangerous and thus needing additional regulation will be putting a thumb on the scale against nanotechnology, deterring companies from using nanotechnology except when no other alternative is available.

There is evidence from an incident in Germany in 2006 that the media and some activist organizations are indeed primed to apply a double-standard to nanotechnology. A new bathroom cleaning product called "Magic Nano" was commercially launched, and within a couple days dozens of people started complaining of "inhalation injuries" and several individuals were hospitalized.[19] Front-page newspaper stories around the world promptly focused on the call by some activist groups for an immediate global moratorium on nanotechnology in light of this apparent hazardous response.[20] Shortly thereafter, the German government announced that "Magic Nano" was misleadingly named and in fact contained no nanotechnology.[21] Concern about the incident, and the consumers who had been harmed by the product, quickly faded. It seems that only injuries caused by a nanotechnology product were of significance; the exact same injuries caused by a non-nano product were not of interest, although to the victims it made no difference whether it was a nano or non-nano product that harmed them. Reflecting on this incident suggests a tendency to preferentially stigmatize and discriminate against nano-products. This incident, and the history of discriminatory regulation and stigmatization of other technology products such as GM foods, indicates the need for a fair and non-discriminatory regulatory approach,[22] much like the principle of international trade law against regulating products based on their "process and production methods" (PPMs).[23]

Lesson 3: Adaptive Regulatory Approaches

A third lesson from the history of technology regulation is that oversight frameworks need to be adaptable and flexible to keep pace with rapidly evolving technologies. As the rate of development of science and technology has accelerated,[24] legislative and regulatory oversight has struggled to keep up-to-date with the technologies they purport to regulate.[25] The Office of Technology Assessment (OTA) noted in 1986 that "[o]nce a relatively slow and ponderous process, technological change is now outpacing the legal structure that governs the system, and is creating pressures on Congress to adjust the law to accommodate these changes."[26]

At the very time that technology is accelerating, both legislative and regulatory decision-making institutions seem to be bogging down and becoming slower. Congress is handcuffed by the synergistic effect of an impossibly large number of important issues needing attention mixed with partisan gridlock, making prompt action on any but the most urgent or symbolic issues unlikely. For most issues, there is little chance of laws being updated except during infrequent policy "windows" in which circumstances align to bring the issue to a brief moment of congressional attention.[27] Once Congress has acted, it may be years or even decades before the issue is revisited by Congress. Similarly, agency rulemaking has been slowed by the myriad of analytical requirements imposed on agencies, the threat of judicial reversal, and the dynamics of interest group politics.[28]

The combination of this legislative and regulatory inertia has resulted in increasingly obsolete regulatory frameworks where statutes do exist (e.g., many environmental problems, such as the lack of effective regulatory authority over non-point sources under the Clean Water Act).[29] Perhaps even worse, for many relatively new technologies, there is no meaningful existing regulatory framework (e.g., embryonic stem cell research, artificial reproductive technologies, preimplantation genetic screening, direct-to-consumer genetic testing, new surveillance technologies, and internet privacy).[30]

Lyria Bennett Moses has identified four potential problems that may result from the failure of law to keep pace with technology, including: (1) the failure to

impose appropriate legal restrictions and precautions to control the risks of new technologies; (2) uncertainties in the application of existing legal frameworks to new technologies; (3) the potential for existing rules to either under- or over-regulate new technologies; and (4) the potential for technology to make existing rules obsolete.[31] For nanotechnology, this "pacing" problem seems particularly acute, given the rapid pace at which the technology is developing: "We have moved into…a …world dominated by rapid improvements in products, processes, and organizations, all moving at rates that exceed the ability of our traditional governing institutions to adapt or shape outcomes. If you think that any existing regulatory framework can keep pace with this rate of change, think again."[32]

It may therefore be necessary to create innovative, non-traditional regulatory oversight models that will be capable of keeping up-to-date with rapidly developing nanotechnologies.[33] As a senior Intel executive testified to Congress:

> What we want to avoid is for the trajectory of nanotechnology to follow that of genetically-modified organisms (GMOs), the most recent 'magic' technology. In the case of GMOs, deployment of applications outpaced attention to the environmental, health, and safety implications of the technology. Public concerns that arose because of this have significantly retarded the realization of GMO's great commercial potential.[34]

One limited approach to this need to keep regulatory oversight up-to-date with rapidly evolving nanotechnologies would be to incorporate some type of procedural timing mechanism in any statute or regulation specifically directed at nanotechnology, such as a sunset provision or a mandatory independent periodic review requirement that forces revisiting the regulatory approach at regular intervals. A more radical approach would be to consider some alternative form of regulatory oversight mechanism, such as the environmental covenants used in the Netherlands[35] or principles-based regulation,[36] both of which provide for a more fluid, evolving oversight system.

Lesson 4: Address Social and Moral Concerns

For many emerging technologies, including nanotechnology, public concerns tend to have a strong social or ethical element, in addition to more traditional health, safety, and environmental concerns that regulation has traditionally addressed. These social and ethical issues include the power of corporations to make unilateral decisions about new technologies that can fundamentally reshape society; fairness and equity concerns about the distribution of new technologies and their benefits; disruptions to the "natural" purity of food, the human body, or nature; and the ever-present "yuck" factor or repugnance in response to technological developments that cause discomfort or unease, at least on first impression, for many citizens.[37]

Whatever the substantive merits of these social and ethical concerns, it is imperative that they be given due consideration in a democratic governance system. Unfortunately, existing regulatory frameworks often exclude consideration of social and moral concerns, ruling them outside the bounds of the jurisdiction of regulatory agencies or reviewing courts. An early example of such preclusion was the initial decision to patent living organisms. Unlike its European counterpart (the European Patent Organization), which applies the "ordre public" (or public morality) clause to deny patents to morally objectionable technologies,[38] the U.S. Patent and Trademark Office is without authority to consider the moral implications of patent applications.[39] Moreover, when various religious, environmental, and animal rights groups filed amicus briefs objecting to the patenting of living organisms on ethical grounds, the U.S. Supreme Court refused to consider such arguments on their merits:

> [W]e are without competence to entertain these arguments….The choice we are urged to make is a matter of high policy for resolution within the legislative process after the kind of investigation, examination, and study that legislative bodies can provide and courts cannot. That process involves the balancing of competing values and interests, which in our democratic system is the business of elected representatives. Whatever their validity, the contentions now pressed on us should be addressed to the political branches of the Government, the Congress and the Executive, and not to the courts.[40]

A similar exclusion of ethical and social concerns occurs in approval decisions by the Food and Drug Administration (FDA), which has jurisdiction over many medical and related products that raise such issues.[41] For example, thousands of members of the public submitted comments to the FDA raising social and ethical concerns about the FDA's proposed decision to approve the marketing of milk and meat from cloned animals.[42] While one could take issue with these claims on their merits, the FDA refused to engage the issues altogether, instead dismissing such claims with a cursory statement that "the agency has not been charged with addressing moral, religious, or ethical

issues associated with animal cloning."[43] Yet, a public opinion poll found that 63 percent of respondents felt (53% felt strongly) that "government regulators should include ethical and moral considerations, in addition to scientific evaluation of risks and benefits, when making regulatory decisions about cloning and genetically modifying animals."[44] The FDA's refusal to consider such concerns is undoubtedly correct in a legal sense, since the agency has only been charged by Congress with ensuring that products are "safe" and "efficacious," criteria which do not seem to incorporate broader ethical or social concerns. Nonetheless, it is problematic and short-sighted to reject out-of-hand the deeply felt views of many Americans who take the time to comment on a proposed action by their government, simply because their concerns are outside the agency's constrained mission.

To be sure, there are reasons why it may be problematic to require regulatory agencies to expressly include moral and social considerations in their decision-making criteria.

Other examples involving emerging technologies likewise suggest a systematic problem of failing to address the moral and social concerns expressed by many citizens. Much of the opposition to GM crops and foods is also based on ethical, social, and religious concerns,[45] yet both the FDA and reviewing courts have refused to give any weight to such considerations.[46] The approval of drugs such as human growth hormone that could be used for enhancement as well as therapeutic applications has also proceeded without any significant consideration of the ethical concerns about such enhancement uses.[47] Even Institutional Review Boards (IRBs), expressly charged with ensuring the ethical conduct of human subject research, are precluded from considering broader social and ethical implications of the proposed research: "The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility."[48]

There is a growing realization that there may be a need to expand the decision-making criteria or create new institutions to expressly consider the moral and social aspects of new technologies. For example, the Department of Health and Human Service Secretary's Advisory Committee on Genetic Testing recommended in 2000 that:

> In the future, tests may be developed that raise major social and ethical concerns. Because FDA's review will focus on assuring the analytical and clinical validity of a test, the agency's capacity to assess the ethical and social implications of a test may not be sufficient. The Secretary should consider the development of a mechanism to ensure the identification and appropriate review of tests that raise major social and ethical concerns.[49]

To be sure, there are reasons why it may be problematic to require regulatory agencies to expressly include moral and social considerations in their decision-making criteria. Unlike safety and efficacy, where people can fairly easily reach consensus on what is a good or bad result (e.g., causing tumors is bad), there is more room for disagreement on what is a good or bad moral or social effect (e.g., people may disagree on whether the [hypothetical] impact of genetic engineering in promoting the consolidation of small family farms into larger, more efficient industrial farms is a favorable or unfavorable outcome). In the same vein, social and ethical risks are more intangible, harder to define and quantify, and thus do not lend themselves to the same type of quantitative analyses common for safety or efficacy determinations.

Other problems likewise justify caution in making our regulatory agencies the deciders of moral correctness. The professional staff of regulatory agencies currently consists primarily of scientists, economists, and attorneys. Should these agencies be staffed much more heavily with ethicists and social scientists? The FDA's reluctance to approve over-the-counter sales of the "Plan B" post-coital contraceptive on what appeared to be moral rather than scientific grounds caused widespread unease and objections.[50] Would we accept a government agency making such moral and social decisions explicitly, especially when the outcome might shift dramatically with a change in administration? And given that ethical and moral concerns are closely tied to religious beliefs for many people, would this create a risk of violating the First Amendment requirement for separation of church and state?

These concerns suggest that it might be problematic to give regulatory agencies direct and express authority to make ethical or social judgments. On the other hand, it may be even more objectionable to avoid these ethical and social considerations altogether. A possi-

ble, initial compromise would be to set up an ethical and social advisory committee within each regulatory agency to weigh in on the ethical and social dimensions of proposed regulatory actions.[51] A potential precedent for such an approach is the European Group on Ethics in Science and New Technologies (EGE), which provides ethical and social advice to the European Commission and other EU governing bodies relating to the ethical aspects of the sciences and new technologies.[52]

Lesson 5: International Harmonization

Regulation of new technologies has historically been at a national (or subnational) level, which is a natural focus given existing legal jurisdictions, decision-making structures, and institutions. This nation-by-nation approach has, however, resulted in inefficiencies and conflicts with regard to some past technologies, due to inconsistencies among national approaches. For example, the sharply different regulatory approaches of the United States and EU toward GM foods have resulted in significant global trade disruptions and disputes.[53] The inter-national and even intra-national jurisdictional discrepancies in embryonic stem cell policies have likewise resulted in a patchwork of different rules and requirements that disrupts scientific progress, stability, and coordination.[54] International differences in digital copyright and internet privacy also create problems, given the increasingly international scope of economic and social activity.[55] These problems — experienced as a result of inconsistent national policies, along with the growth of inherently international issues such as climate change and assigning internet domain names — have created a growing interest and emphasis on mechanisms for international harmonization of technology oversight systems.

International harmonization can provide additional benefits beyond minimizing disruptions to global trade and scientific coordination. First, many materials cross national boundaries, either as manufactured products sold in commerce or as environmental contaminants in the air or water. A consistent set of safety and environmental standards across jurisdictions may therefore enhance protection of human health and the environment. Second, multinational companies that manufacture or handle materials such as nanotechnology will benefit from the efficiency and consistency of harmonized regulatory requirements in a global marketplace. Third, international harmonization can prevent a "race to the bottom" or "risk havens" in which some nations may refrain from taking appropriate regulatory oversight in order to attract companies to locate in their jurisdiction.

International harmonization can proceed using one of two sequencing options. The first approach would be to adopt national regulations first, followed by a subsequent phase that seeks to harmonize the pre-existing national regulations. Francis Fukuyama appears to endorse this approach when he writes: "[R]egulation cannot work in a globalized world unless it is global in scope. Nonetheless, national-level regulation must come first. Effective regulation almost never starts at an international level…."[56] But developing national regulations prior to pursuing international harmonization has two costs. First, it delays international harmonization until after national responses have been adopted and implemented, which could result in substantial delays. Second, and more significantly, international harmonization may be more difficult in the face of entrenched and inconsistent national regulations. This was the case, for instance, with regulations of GM foods, where both the United States and Europe were unwilling to back down from their regulatory approach and be perceived as acceding to the contrary approach of the other.

Of course, international regulation is extremely challenging given the many players and their technological, economic, political, and social differences. Incremental international harmonization, such as development of a framework agreement or other "soft law" approaches, may be the most effective way to begin international harmonization from the "ground up" for an emerging technology such as nanotechnology.[57]

Conclusion

Although nanotechnology is relatively new, attempts to regulate emerging technologies are not, as we have now compiled significant experience and learning about the challenges and opportunities of regulating technology. The five lessons briefly summarized here are examples of such learning, and no doubt there are many more lessons and perspectives that can be gleaned from the growing empirical record on technology regulation. While Edmund Burke warned that "[y]ou can never plan the future by the past,"[58] it is nevertheless true that by looking backwards in time, we can learn much that can inform and enlighten our look forward at the emerging nanotechnology era and its regulatory oversight.

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ORIGINAL PAPER

Risk Management Principles for Nanotechnology

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Abstract Risk management of nanotechnology is challenged by the enormous uncertainties about the risks, benefits, properties, and future direction of nanotechnology applications. Because of these uncertainties, traditional risk management principles such as acceptable risk, cost–benefit analysis, and feasibility are unworkable, as is the newest risk management principle, the precautionary principle. Yet, simply waiting for these uncertainties to be resolved before undertaking risk management efforts would not be prudent, in part because of the growing public concerns about nanotechnology driven by risk perception heuristics such as affect and availability. A more reflexive, incremental, and cooperative risk management approach is required, which not only will help manage emerging risks from nanotechnology applications, but will also create a new risk management model for managing future emerging technologies.

Keywords Nanotechnology · Regulation · Risk management · Risk perception · Heuristics · Voluntary programs

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Introduction

Nanotechnology presents both an unprecedented challenge and an unparalleled opportunity for risk management. On the one hand, nanotechnology does not "fit" traditional risk management models, thereby impeding effective actions to manage nanotechnology risks using those existing approaches. On the other hand, nanotechnology will force risk managers to devise innovative new risk management approaches that may be applicable to other emerging technologies in the future.

As nanotechnology has emerged from the laboratory into industrial manufacture and commercial distribution, the potential for human and environmental exposure, and hence, risk, have become an increasing reality and priority. For purposes of this paper, we focus on the health, safety and environmental risks of nanotechnology, rather than more socio-economic or future risks such as privacy, terrorism, and economic displacement. As discussed below, the difficulties in identifying, never mind quantifying, the health, safety, and environmental risks of nanotechnology are a major impediment to applying traditional risk management approaches to nanotechnology. Risk management of nanotechnology is further challenged by the broad range of technologies and products encompassed within the term "nanotechnology," both in terms of current products and applications and even more in terms of future generations of products [26, 55]. The rapid

pace of development of nanotechnologies, the difficulty in defining nanotechnology, and the substantial potential offsetting health and environmental benefits of some nanotechnology applications further complicate risk management of nanotechnology. Finally, risk management of nanotechnology must take into account public perceptions about the risks and benefits of nanotechnology and the growing public demands for regulatory oversight.

This paper analyzes the applicability of traditional risk management principles and new approaches based on the precautionary principle to nanotechnology, and finds these available approaches to be inadequate and unworkable. Nanotechnology will therefore require and force the development of new risk management models, an example of which we suggest here.

Existing Risk Management Principles

Both traditional risk management principles such as acceptable risk, cost–benefit analysis, and the feasibility principle, along with more recent innovations such as the precautionary principle, are inadequate to meet the risk management challenges presented by nanotechnology.

Traditional Risk Management Principles

The three most common traditional models for risk management of hazardous agents are (a) acceptable risk, (b) cost-benefit analysis, and (c) feasibility (or best available technology). *Acceptable risk* approaches rely on risk assessment to describe the risks of an agent, and then seek to reduce risks to levels that are socially acceptable. Current understanding of nanotechnology risks is too uncertain to permit meaningful risk assessment, and is likely to remain so for some time [11, 37, 43, 44, 48, 56]. There are no accepted test methods or validated data that can be used to prepare scientifically credible quantitative estimates of risk of specific nanotechnology applications at this time [59, 73].

Some initial animal studies have indicated the potential for toxicity in at least some nanomaterials, but these studies are very preliminary involving very high exposures that do not permit human risk assessment [47, 73]. Moreover, the initial studies give early indications of the likely complexity of nanotechnology risk assessment. For example, different forms of single-walled nanotubes present strikingly different risks depending on the manufacturing process and facility [37, 77]. The toxicity of nanomaterials appears to be determined by a complex set of characteristics, including size, surface area, chemical composition, coating, shape, and route of exposure [47, 48, 73]. Given this complexity, extrapolation of toxicological properties from other materials, including other nanomaterials, is currently unreliable, requiring risks to be determined on a case-by-case basis [19, 22, 59], a daunting prospect given the hundreds of nanotechnology products currently on the market and the thousands more to come.

Not only are risk-based approaches infeasible from a scientific perspective, they are also legally suspect, as regulators generally lack the risk information they need to make the threshold findings required to take regulatory action under, for example, most US environmental statutes [19]. The nanotechnology risk assessment dilemma is thus aptly summarized by Kristen Kulinowski, Executive Director of the Center for Biological and Environmental Nanotechnology: “We are in this awkward middle territory where we have just enough information to think there is an issue, but not enough information to really inform policymakers about what to do about it” (quoted in 46).

Another complication is the rapid pace of nanotechnology development, which is rapidly outpacing the development of risk assessment for these technologies [56]. For example, even though hundreds of nanotechnology products are already on the market, some involving significant exposure to workers and consumers, the US Environmental Protection Agency’s recently issued White Paper on nanotechnology provides a timeline for oversight, in which it will not be until the year 2011 or 2012 that the agency has sufficient risk knowledge to develop a systematic approach for managing the risks of nanotechnologies ([77], p. 112). Of course, by that time, virtually every citizen will have been exposed to nanomaterials, and new generations of nanotechnology products will be entering the market, creating new risk uncertainties. As David Rajeski of the Woodrow Wilson Center warns, “[i]f you think that any existing regulatory framework can keep pace with this rate of change, think again” ([55], p. 45). This is not to say that the development of risk assessment approaches for

nanotechnology is not needed, but only that we cannot rely on risk-based approaches to provide the primary risk management solution in at least the short-term for such a rapidly emerging technology.

Finally, acceptable risk approaches generally suffer from a structural disadvantage: by only considering risks and their acceptability, they disregard other important factors such as the benefits of the technology creating the risks and the costs of reducing risks. As discussed below, these factors are likely critical for socially optimal decisions about nanotechnology.

A second traditional risk management model is *cost–benefit analysis* or balancing, in which the costs and benefits of proposed risk management options are balanced. Unlike the acceptable risk model, the cost–benefit model has the advantage of considering both the benefits and risks of nanotechnology, which is important given that nanotechnology is likely to present both risks and benefits for public health and the environment [19]. Nonetheless, the cost–benefit model is ill-equipped for managing nanotechnology at this time, given the immense uncertainties about its risks and benefits.

The enormous number and diversity of potential nanotechnology applications also make this approach unfeasible—a global cost–benefit balancing for nanotechnology as a whole would mask the significant cost–benefit variance that likely exists between different applications. Alternatively, performing separate cost–benefit balances for each specific nanotechnology application would likely overwhelm available risk management resources given the large number of potential applications. While some qualitative weighing of the risks and benefits of nanotechnology may be a useful exercise for purposes of thinking about how those risks should be managed, cost–benefit analysis does not provide a workable risk management approach for nanotechnology at this time.

The third and final traditional risk management principle is the *feasibility* or *best available technology* approach. This approach, which requires reduction of risks to the lowest level technologically or economically feasible, has the advantage of not requiring information about risks or benefits. Indeed, the feasibility approach has achieved considerable popularity among policymakers in recent years because it allows circumvention of controversies over risk analysis and jumps straight to reducing risks to the extent possible [5, 14, 61, 78]. Given the enormous uncertainties about nanotechnology risks, this approach has some appeal. The strength of the feasibility approach is also its key weakness, however, because, while ignoring risk information avoids controversy, it also avoids addressing what is truly important, which is risk [45, 66]. The feasibility approach thus may over-regulate or under-regulate risks depending on whether the best available technology is necessary or sufficient to reduce unacceptable risks. This problem could be particularly problematic for an emerging technology such as nanotechnology.

Moreover, it is not at all clear how the best available technology approach could or would work for nanotechnology. Certainly, the application of work practices and other precautions that seek to limit exposure to nanomaterials appears sensible. But we may not know enough to go further and require technology controls on production processes, including pollution control of emissions, when we know so little about the nature, level, controllability, and risks of released nanoparticles. It is also difficult to apply a best technology approach to the growing number of nanotechnology consumer products given that the public's use and disposal of such products is difficult to control. Finally, a best available technology approach deters companies from developing better control technologies, since doing so will only result in more stringent (and hence costly) regulations [2]; this is the wrong incentive for a rapidly emerging technology such as nanotechnology [57].

In sum, none of the three traditional models of risk management are capable of effectively managing the risks from nanotechnology at this time given the tremendous uncertainties that exist for this emerging technology. This realization has prompted some to advocate application of the most recent entry in the risk management toolbox, the precautionary principle.

The Precautionary Principle

Numerous public interest groups and scholars have called for the precautionary principle to be applied to nanotechnology [17, 21, 27, 38, 79]. The precautionary principle, which has emerged in recent years as an alternative approach to risk management, is often summarized by the phrase "better safe than sorry." The precautionary principle recognizes that health and environmental decisions often must be made in the face of pervasive uncertainty, and therefore calls on

decision makers to err on the side of safety by delaying new technologies until their safety can be adequately ensured. This requirement is often framed in terms of shifting the burden of proof to the proponent of a technology to demonstrate its safety. Given the massive uncertainty about nanotechnology risks, this technology might appear to be an ideal candidate for application of the precautionary principle. Yet in fact nanotechnology vividly demonstrates the limitations of the principle as a decision-making tool; the precautionary principle too is not a workable risk management model for nanotechnology.

The first problem with the precautionary principle is that it is too poorly defined to serve as a decision-making rule. While lawmakers and proponents frequently cite to "the" precautionary principle, there is no standard text for the principle, and the dozens of formulations that have been suggested differ in important respects [52]. Moreover, no version of the precautionary principle answers the critical questions that need to be considered in moving forward with regulatory decisions, such as what level or type of evidence (if any) of harm is sufficient to trigger the principle, what quantum and types of data must a manufacturer produce to satisfy the principle, what level of risk is acceptable, and how should the benefits of a technology be weighed against its risks (if at all; [40]). Without any criteria or guidelines to resolve these questions, the precautionary principle is prone to arbitrary and capricious decision-making, if not outright mischief. Examples of such unreasonableness include the invocation of the precautionary principle to ban corn flakes enhanced with essential vitamins in The Netherlands, prohibit caffeinated energy drinks in France, prohibit cranberry juice beverages in Denmark because they contain vitamin C, and reject food aid containing some genetically modified corn in the famine-affected nation of Zaire [41].

The precautionary principle suffers from another flaw in that it is biased toward the status quo, impeding new technologies even if they may ultimately prove beneficial for the environment or public health [12, 25]. It is quite possible that a freeze or moratorium on nanotechnology per the precautionary principle would do more harm than good to human health and the environment, never mind the many other benefits of nanotechnology that would be forgone. Nanotechnology offers many promising health and environmental benefits, including more effective and safer cancer treatments, improved medical diagnostics, remediation of hazardous wastes, cleaner energy sources, and improved control of pollution emissions [24, 77]. Given these potential benefits, precaution and emphasis on protecting health and the environment might actually weigh in favor of promoting rather than restricting nanotechnology. The precautionary principle fails to provide guidance on which direction to pursue [69, 70]. Finally, there is evidence that application of the precautionary principle increases, rather than addresses, the public's concerns and anxiety about a technology [82], and thus cannot be defended on the instrumental ground of enhancing public assurance.

Some have suggested that the precautionary principle makes the most sense for protecting against "catastrophic risks" that could irreversibly destroy major parts of the human population or the earth's ecosystem [72]. This argument has been applied to nanotechnology. For example, two weeks after the 9/11 terrorist attacks on the United States, the *New York Times* published an article debating whether, in light of the horrific application of a generally peaceful technology demonstrated by the 9/11 attacks, humanity might be better off in the long run to forgo a powerful new technology such as nanotechnology that could be used for enormous good or evil [34]. Commentators such as Bill Joy have speculated that nanotechnology could be used to develop swarms of self-replicating nanobots that could destroy the planet, often referred to as the "grey goo" scenario [29]. Applying the precautionary principle to this possibility, the argument goes that no amount of potential benefits from nanotechnology would justify assuming a risk (no matter how small) of such a catastrophic consequence.

There are several problems with this nano-catastrophism argument. First, virtually all serious analyses of the grey goo scenario—including a recent analysis by Eric Drexler, who first posed the problem [13]—have concluded that it is extremely implausible if not impossible [51]. Second, catastrophic scenarios can be envisioned for virtually any technology, but we would be paralyzed into inaction if we avoided any technology that could be associated with such a scenario, no matter how implausible. The first environmental release of a genetically modified organism, the so-called ice minus bacterium, was alleged to create the risk of destabilizing global

climate by spreading throughout the upper atmosphere and disrupting the normal cloud seeding processes [30]. The new particle accelerator built for the Brookhaven National Laboratory in 2000 allegedly could have produced a shower of quarks that might have turned the entire earth into some new type of matter [53]. Any given international traveler could conceivably have inoculated himself with the smallpox virus and entered the country with the intention of starting a devastating pandemic, a catastrophic risk that could only be prevented by banning all international travel. While preventing catastrophic risks should be a top priority, it would not be practical to allow the mere possibility of some remote catastrophic risk to be a sufficient rationale for banning a promising technology [53, 72].

Finally, while it may be possible to imagine potential catastrophic risks from nanotechnology, it is also possible to envision potential future applications of nanotechnology that could save us from other catastrophic risks. For example, medical applications of nanotechnology may give us the tools to stave off the next pandemic virus that could be mutating in some distant corner of the world right now. Or nanotechnology may be used to protect us from some asteroid hurtling through space on a path that will intercept the earth sometime in the future. While these scenarios may be remote, so too are the catastrophic scenarios for nanotechnology. Truth be told, no one knows for sure which of these implausible scenarios are the most implausible. Banning nanotechnology based on the precautionary principle could just as easily prevent as create a future catastrophic risk to humankind. Thus, while the precautionary principle provides a useful general philosophy, and while some application of precaution is certainly appropriate to guide the development of nanotechnology, the precautionary principle itself fails to provide a workable risk management approach.

In sum, neither the traditional risk management principles nor the new precautionary principle provides an acceptable approach for regulating nanotechnology. For past technologies, that would normally have meant that risk regulation would be postponed until further evidence of a real problem had emerged [19, 37, 83], perhaps with the interim use of some secondary risk management tools such as risk communication, liability, self-regulation, and insurance [6, 26].

For the same reasons, it is perhaps not surprising that, despite the enormous attention given to nanotechnology in recent years, no national government has yet enacted any traditional nano-specific regulation [8, 9].

Public Perceptions of Nanotechnology Risks

As the previous section demonstrated, anticipatory regulation of nanotechnology pursuant to current models appears inappropriate and ill-advised. It is equally inadvisable, however, for regulators to sit back and do nothing. As we have previously noted, legal regulation of nanotechnology is inevitable [42]. The ethical, environmental, and economic issues that nanotechnology raises, whether probable or fantastical, will necessitate some regulatory response, if only because of political pressure. The public is already making up its mind about nanotechnology's risks and benefits, and they are doing so on the basis of very little information [3, 31, 50, 62].

The public's willingness to form premature opinions about nanotechnology's benefits and risks may jeopardize the development of the technology. As one commentator put it, "[o]ne of the greatest challenges facing nanotechnology is avoiding a backlash from the public that slows or even halts the progress of research and development." ([62], p. 335). This experiential concern, derived from examples of public backlashes against other technological developments including genetically modified organisms, nuclear power, and recombinant DNA technology, merges with another area of research on how the public forms opinions about risks in the face of uncertainty.

Decades of research into risk perception have discovered a series of cognitive and emotional responses that influence how individuals perceive risks. Unlike prior models of human cognition as calculating, rational, and logical, this research has revealed that individuals employ "heuristics," mental short-cuts based on experience and emotion, to assess potential risks and benefits. Although these heuristics work well in many cases, they are especially vulnerable in cases of uncertainty, where they are prone to systematic and predictable errors.

Adding to the concern that individuals may make skewed determinations of risk based on heuristics is the fact that such decisions are not made in a vacuum. Social interactions, for example, play an important

role in the formation and reinforcement of heuristic reasoning [31, 71]. As a result, reactive media attention and the concerted actions of public interest groups can directly affect how individuals initially perceive risks—often resulting in the cementing of opinion on a given technology's risks and benefits, making that opinion exceedingly difficult to change and often resulting in extreme positions [31, 64].

The danger that nascent public opinion on the risks and benefits of nanotechnology will be inappropriately informed by unbalanced media attention, reinforced by social interactions, and cemented into extreme positions of fear and dread is certainly real. Worse yet, there is growing evidence that many individuals are predisposed to fear nanotechnology, as demonstrated by the over-reaction to the initial (but false) reports that people made ill by the German cleaning product "Magic Nano" were the first demonstrated injuries from a nanotechnology product (it was subsequently revealed that, despite its name, Magic Nano was not a nanotechnology product) ([83], p. 704; [75]).

The decades-long research of behavioral scientists has led to one unmistakable conclusion—human beings seldom assess uncertain risks based solely on information, probabilities, or logical assessment. When confronted with questions such as, "will rapidly advancing nanotechnology revolutionize health-care, the nature of computers, and the structures of materials, or will it lead to as yet uncontemplated new forms of pollution and cancer," ([39], p. 119) people do not wait until they have information to make an assessment. Instead, people rely on heuristics to make a quick, intuitive, and at times emotional assessment about the likelihood a given risk will occur. In place of rational assessment, behavioral science posits that "people rely on a limited number of heuristic principles which reduce the complex tasks of assessing probabilities and predicting values to simpler judgmental operations" ([76], p. 3). In this way, heuristics "play a role in aiding individuals in ascertaining the relative risks posed by future events without resorting to more accurate, but time consuming, statistical analysis" [74]. Unfortunately, "heuristics serve people well in many circumstances, but they also create vulnerabilities to the predations of advertisers, political spin doctors, trial attorneys, and ordinary con artists" ([54], p. 1165).

The research into risk perception has identified numerous common heuristics that people employ to assess risks and benefits. For example, in many cases people react to possible risks by focusing solely on the type of harm rather than the probability of harm (probability neglect) [68]. In other situations, when confronted with actual harms, individuals seek human causes and downplay the possibilities that chance and nature are responsible (the mythical benevolence of nature; [69, 70]. Finally, other researchers have concluded that individuals cannot simultaneously perceive that individual technologies have both benefits and risks, and as a result cognitively privilege benefits to the exclusion of risks or vice versa (cognitive dissonance avoidance; [39]). These are but a few of the cognitive and emotional processes that researchers have identified as affecting risk perceptions [52]. The key to understanding these heuristics and biases is to see that individuals do not arrive at them analytically: they are knee-jerk, unreflective, intuitive, reactive, and experiential.

The most important of these heuristics for nanotechnology is "Affect." First introduced by Paul Slovic, the Affect heuristic "refers to people's tendency to rapidly and automatically have positive or negative feeling when confronted with a certain word, concept, or other stimulus" ([39], p. 161). In other words, individuals have a predisposition, most likely unconscious, towards various stimuli. When confronted with such a stimulus, individuals react to it affectively [28, 31, 52, 63, 65, 67, 70, 76].

An interesting effect of the Affect heuristic is the tendency of individuals to negatively correlate a technology's perceived risk with its benefit. In other words, numerous studies have shown that where individuals believe a technology has high benefits, they automatically believe its risks are low. Conversely, where risk is perceived to be high, the benefits are correspondingly seen as low. This negative correlation has been shown to affect both lay and expert opinions, and is robust even in the face of countervailing evidence [63]. Based on this finding, researchers hypothesize that individuals possess an emotive and ingrained response to various stimuli. In short, how individuals *feel* about a particular stimulus directs how they perceive its dangers or benefits [63].

The question, of course, is how do people arrive at these affective orientations? In many cases, individuals do not assess technologies as separate risks (or benefits), but instead adopt a world-view that automatically, or "affectively," views technology as risky [63]. A recent

study by Kahan et al. [31] investigated the role that Affect played in determining assessments of nanotechnology risks. According to Kahan, "the visceral, emotional responses of our subjects, pro or con, determined how beneficial or dangerous they thought nanotechnology was likely to be…" ([31], p. 3).

Of some comfort to those interested in nanotechnology is the finding that "these instantaneous judgments were not static. Individuals exposed to information on the risks and benefits of nanotechnology formed different views from individuals not so informed" ([31], p. 3). Less heartening, however, was the finding that "the *ways* in which information influenced our subjects—whether it inclined them to see nanotechnology as more risky or more beneficial—was highly conditional on the values they held" ([31], p. 3). Thus, individuals who viewed themselves (or, better put, were affectively inclined) as hierarchical or egalitarian, individualistic or communitarian, interpreted information about nanotechnology risks and benefits to *conform* to their affective dispositions. The fact that Affect so deeply guided individual views on the risks or benefits of nanotechnology, even in the face of evidence contrary to their initial beliefs, led Kahan and others to conclude:

> These results paint a picture … of at least one possible future for nanotechnology. It is one in which citizens rapidly take affect-driven positions, which harden as they conform what they learn thereafter to their more basic cultural attitudes toward technology and risk. The result is likely to be a state of political polarization over the desirability of nanotechnology that very much resembles the one that now exists for other controversial environmental issues, including nuclear power and global warming. Or at least that is how things are likely to play out absent the development of strategies that neutralize the tendency of persons to assimilate information in a manner that confirms their emotional and cultural predispositions ([31], pp. 3–4).

The bleak picture painted by this study is made worse when we consider a second common heuristic, "Availability." The Availability heuristic is among the most widely studied and has achieved the most attention in legal circles. Although it is employed in numerous aspects of cognition, its chief role is in assessing the *likelihood* of risks. [76]. According to researchers, individuals who can easily recall a memory specific to a given harm are predisposed to overestimating the probability of its recurrence, compared to other more likely harms to which no memory is attached. In other words, "the availability heuristic captures the mental process by which people assume that events more easily recalled are more likely to recur" [74]. A classic example of Availability is that individuals who have seen or read about a house burning down are more likely to believe their own house will burn down than: (a) they were prior to witnessing the event, and (b) others who have not shared a similar experience.

The nature of the initial experience also determines the influence of the Availability heuristic on the assessment of recurrence probabilities. Thus, "[t]he impact of seeing a house burning… is probably greater than the impact of reading about a fire in the local paper" [74]. The recency of an experience also affects the level of risk individuals assign to a given event.

Numerous factors affect individual recall and Availability, including suggestion, memorization, recency, and the amount of information recalled. If we are to take the existence of the Availability heuristic seriously, we must assume that the subjective perception of risk for a given event or policy may be linked to the respondent's experiences, with some experiences having a more direct effect than others; "availability may be endogenous to individual predispositions" ([69, 70], p. 759).

An important point for understanding these heuristics is that each is sensitive, perhaps keyed into, the imagery and meaning associated with a given risk; and imagery and meaning are deeply affected by social interactions. With Affect, the imagery and perception of a risk may be endogenous, but can be influenced and exacerbated by social interactions [63, 69, 70]. With Availability, the imagery and meaning attached to a risk are by definition found in public messages and experiences. The effect that external imagery and social reinforcement can have on individual perceptions of risk has led many to conclude that the media, public interest groups, industry, and government have real power to influence the public's perceptions about the nature and probability of risk associated with a given technology.

Many have noted, and it is indeed intuitive, that as media attention and the actions of interested parties continually emphasize certain risks, especially when

they tend to stigmatize the relevant technology, it is possible for such images to overwhelm objective and balanced information about true probabilities and harms. Thus, there are real incentives for those who oppose implementation of a new technology (for whatever reason) to highlight images that evoke dread, fear, disgust, and similar emotions (cf. "Frankenfood"). Where political actors are able to persistently project such images, technologies may be stigmatized as inherently dangerous [33]. Once so stigmatized, "vivid images and concrete pictures of disaster can 'crowd out' other kinds of thoughts, including the crucial thought that the probability of a disaster is really small" [69].

The real importance of stigmatization is that it has effects far beyond the individuals who may be convinced of the dangers of a given technology or application. As just noted, individuals form perceptions of risk based in large measure on social interactions with peer groups [63]. Thus, "representative anecdotes and gripping examples can move rapidly from one person to another. Once several people start to take an example as probative, many people may come to be influenced by their opinion, giving rise to cascade effects…[a] problem [that] might well be aggravated by certain media and new technologies" ([70], p. 759). Cascade effects are most closely associated with Availability, but can also have impacts on Affect by reinforcing affective dispositions and associating technologies with specific risks that individuals are affectively predisposed to fear or loathe ([33, 81], p. 27, [23, 35, 54, 63], p. 221).

Nanotechnology is especially susceptible to cascade effects and affective hardening of positions. The experiences of GMOs and other "controversial" technologies have led political actors to consciously highlight dreaded harms and to persistently publicize anecdotes that reinforce the availability of such harms in connection with new technologies like nanotechnology. As a result, some now believe that "functional discourse… is largely absent from technology debates, and the climate necessary for productive discourse is poisoned" ([39], p. 117). Indeed, in the case of nanotechnology, some already believe that "the only messages… currently reaching the public are negative ones portrayed in movies and television…" ([62], p. 335). Media depictions of nanotechnology tend to emphasize fantastical risks, including widespread environmental degradation, increased cancer, and even the destruction of the human race [62]. In the face of such overwhelming negative publicity, it is quite likely that nanotechnology will be subject to availability cascades, strongly anti-nano affective attitudes, and overestimates of the probability of specific risks.

This bleak picture is not, however, the only possible future for nanotechnology. Although we have focused here on the ways in which heuristic processes may lead to overestimation of risks, it is equally possible that individuals may focus on benefits. Availability cascades and affective attitudes may also produce perceptions of the benefits of the technology as overly probabilistic and overly desirable. If available imagery and affective reasoning (and messages sent to appeal to such reasoning) strongly support the technology, these may offset risk-based reasoning or even overwhelm it.

Of course, no one yet knows whether nanotechnology's risks do outweigh its benefits. What is clear, however, is that fear-based, or risk-focused, attention to nanotechnology has recently begun to outweigh attention to its potential benefits [62]. In order to keep open the possibility of a reasoned discourse on the risks and benefits of nanotechnology, therefore, some action must be taken to reassure the public that nanotechnology risks are being actively managed, while avoiding the pitfalls of anticipatory regulation under pre-existing models. As Cass Sunstein has noted, "Government should take action that reassures people, even if such actions are not justified on technical grounds" [64, 70].

The question is, what action? In the next section, we outline a plan for a gradual, flexible, and evolutionary approach to nanotechnology regulation that we believe would be an important first step in restoring balance to the discourse on nanotechnology risks and benefits, while reassuring the public that steps are being taken to identify and control those risks. Our approach is consistent with a developing consensus among regulatory scholars that a non-traditional "soft law" approach that is incremental, reflexive, and cooperative will be needed to manage the risks of nanotechnology, at least in the near future [7–9, 18, 20, 36, 37, 49, 57, 60, 80, 83; but see 27].

New Risk Management Model

Given the pervasive uncertainty and dynamism of current nanotechnology developments, we suggest a

flexible, evolutionary approach to risk "regulation," especially in the immediate, near and medium terms. The approach we suggest is flexible in two senses. Substantively, it draws on multiple approaches to addressing risk, not only the accepted models of risk regulation discussed above, but also more general approaches to the appropriate handling of risky technologies, such as the notion of product stewardship and the professional ethics of researchers. Procedurally, as these examples suggest, our approach favors subsidiarity and decentralization: the participation of a wide range of private and public stakeholders, including those currently researching and commercializing nanotechnology, in developing and applying risk management norms. Broad stakeholder participation should help us gain a better understanding of the actual risks and benefits of particular nanotechnology products and processes, communicate that understanding to the public, and enable multiple approaches to managing risk. Over time, the experience and learning these approaches produce should allow societies to gradually develop appropriate and cost-effective systems of regulation.

While no regulatory approach can overcome all the heuristics that distort individuals' assessments of risks, this approach does address some of the major issues. Our approach emphasizes transparency and dissemination of information to the public by all participating actors; in addition, it emphasizes active participation of stakeholders, including public interest groups, in developing and applying risk management norms. The result would be to create and disseminate accurate images, and even actual experiences, of the benefits, risks, and probabilities associated with nanotechnology. Transparency and participation would be ongoing, providing regular updating of availability perceptions. In addition, this approach would demonstrate to concerned onlookers that multiple actors, from academic researchers to manufacturers to government agencies, are actively identifying and addressing potential risks through a range of techniques. Finally, if properly managed, this approach should generate an increased level of public trust in those responsible for the development of nanotechnology.

As noted above, the current risk status of nanotechnology is dominated by uncertainty. Many potential environmental, health, and safety risks are uncertain in terms of severity, threshold exposure levels, variations among even closely related products and processes, and the like; other risks are "unknown unknowns." A lack of definitional certainty as to what exactly constitutes nanotechnology exacerbates this uncertainty and hampers efforts to identify and address the risks of particular applications, technologies, and research processes.

Despite this pervasive uncertainty, the growing political pressure to regulate and the need to control social responses mean that some form of regulatory response will likely be required in the near future. Since nanotechnology R&D, manufacturing and other activities are proceeding apace, it is important to begin immediately to develop ways to deal with the potential risks, whether fully actualized or merely perceived.

Theoretical Background

Although traditional models of technology risk regulation are inappropriate for the reasons discussed above, lessons from the broader study of regulation are highly relevant. One of the most influential recent works in that literature, Ayres & Braithwaite's *Responsive Regulation* [4], provides the theoretical inspiration for our approach.

Responsive Regulation was written at a time of widespread debate about the merits of "deregulation." Ayres & Braithwaite, however, argued that the choice between "regulation" (understood as traditional command and control) and "deregulation" is a false one: Regulation always involves a symbiotic relationship between public and private actions, and the interactions between these two realms can be managed, responding precisely to varying conditions and behavior across industries and even firms, to obtain better regulatory outcomes. Their emphasis on substantive flexibility and subsidiarity or decentralization mirrors our own views on appropriate risk regulation for nanotechnology.

Ayres and Braithwaite employed the construct of a "pyramid" to illustrate their flexible approach to regulation. Most narrowly, this pyramid depicts the spectrum of possible *sanctions*—from persuasion and warnings, at the base, up through civil, licensure, and criminal penalties, at the peak—available to regulatory agencies. A broader version of the pyramid captures the range of regulatory *strategies* available at the national level—from self-regulation at the base,

through supervised or enforced self-regulation and other forms of public–private interaction in the middle, to standard forms of command-and-control regulation, still with a range of possible penalties as depicted on the original pyramid, at the peak (Fig. 1).

With this tool kit at hand, regulators can play a tit-for-tat strategy: they allow firms to self-regulate so long as the firms reciprocate with responsible action; if instead some firms act opportunistically, regulators respond to the defectors with appropriate penalties and more stringent regulation. The threat of regulatory intervention both deters non-compliance by potential defectors and encourages all firms to develop an attitude of social responsibility. If this strategy is skillfully deployed, the majority of regulatory activity will occur near the base of the pyramid, at the lowest levels of governmental intrusion (e.g., persuasion or self-regulation), with more intrusive actions taken only when softer measures prove unworkable.

Recent scholarship has attempted to apply the regulatory pyramid to nanotechnology. Bowman and Hodge [9] use a pyramid model to argue for a complex regulatory system for nanotechnology (Fig. 2). Their pyramid is hexagonal, with six sides that correspond to families of issues including occupational health and safety, environmental protection, product safety, privacy and civil liberties, intellectual property, and international law. In addressing each set of issues, the pyramid suggests that regulators should deploy a range of regulatory options, from "soft law" to "hard law," as called for by Ayres & Braithwaite [4].

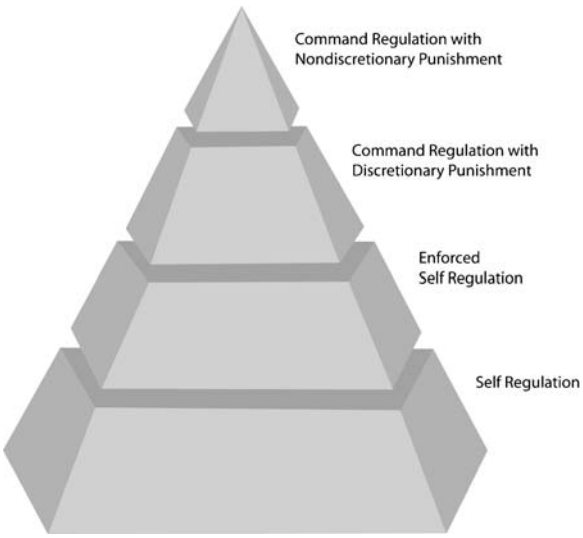

Fig. 1 Ayres & Braithwaite regulatory pyramid (adapted with permission from Ayres and Braithwaite [4]

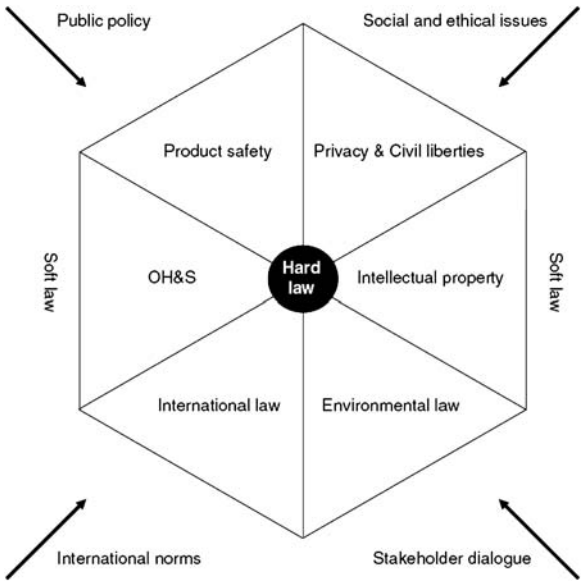

Fig. 2 A conceptual model for the regulatory frontiers of nanotechnology. Source: Bowman and Hodge [7]

While the pyramid model provides the theoretical inspiration for our approach, both the Ayres/Braithwaite and Bowman/Hodge models are largely static: they envision a fully developed regulatory system that can effectively manage a particular set of risks. Both models, moreover, are designed for advanced nations with highly developed legal systems, in which legislatures and agencies can create, communicate, and utilize a range of regulatory options. Finally, both at least implicitly assume high levels of information and understanding on the part of regulators. As such, both models may better depict a potential future regulatory end state than an immediate approach capable of addressing the risks of a dynamic technology in an environment of pervasive uncertainty, as is the case with nanotechnology.

Incremental Regulation

The concepts behind these models, however, can be deployed in a different way to address the uncertain risk situation of nanotechnology today. Rather than viewing persuasion, soft law, self-regulation, command-and-control regulation and the like as components or "layers" within a static regulatory system, we extend the regulatory pyramid through time, viewing these approaches as sequential.

In the near term, we would begin with softer and more decentralized measures, including self-regulation. We would emphasize those measures that will produce the greatest information, coupled with mechanisms for learning from them. As in the original pyramid model, such soft regulatory strategies are the most flexible and the least costly and intrusive. To be sure, however, in a sequential approach the initial stages will not be subject to the ongoing agency oversight and threat of tit-for-tat regulatory intervention that characterize a fully developed regulatory system; the risk of opportunism undoubtedly exists. That risk is the principal basis for criticizing incremental or soft law approaches. For example, in proposing a set of "Principles for the Oversight of Nanotechnologies and Nanomaterials," a coalition of civil society organizations recently argued: "Voluntary approaches are wholly inadequate to oversee nanotechnology. Voluntary programs lack incentives for 'bad actors'… to participate, thus leaving out the entities most in need of regulation" [27].

Yet there are other incentives for responsible action by those involved in nanotechnology. These include the need to overcome public fears and avoid reputational costs, stigmatization, and backlash; the risk of costly litigation and liability; and the desire to forestall inappropriate mandatory regulation. To a considerable extent, these social forces fill the role of the regulator's tit-for-tat strategy. Some actors, such as scientific researchers, are influenced by professional norms of responsibility, quite apart from legal incentives. Civil society organizations can pressure those working with nanotechnology to adopt responsible approaches, and can participate in multi-stakeholder programs; soft regulation need not be limited to self-regulation.

In addition, as we argue below, even in the near term we would encourage regulators and other public officials to promote responsible private actions and steer them in desirable directions (for example, by encouraging transparency and participation, two other principles proposed by the coalition); fund research on the risks of nanotechnology (perhaps focusing on broader and longer-term risks that private actors have weaker incentives to consider); and take other supportive actions short of mandatory regulation.

Finally, the call for immediate regulation overlooks two countervailing considerations. The first is the social cost of regulation that is inappropriately designed; the risk of design error is quite high, since immediate regulation would almost inevitably be based on one of the existing risk management approaches we have criticized as inadequate. The second is the difficulty of achieving political consensus and action on specific forms of regulation—even in one country, let alone on a harmonized basis across countries. Soft approaches may lack the potency of mandatory law, but they are often much easier to put in place.

Over time, as society learns about the actual risks and benefits of nanotechnology from its early experiences with state-supported voluntary measures, a regulatory end state similar to the Aryes/Braithwaite and Bowman/Hodge pyramids can be gradually built up. All stages of this approach should be managed with a high degree of transparency and stakeholder participation, to provide accurate images of risks, benefits and probabilities, build trust, and set the stage for an effective regulatory system.

Figure 3 provides a rough graphical depiction of our incremental approach. We suggest only a few broad regulatory categories in Fig. 3, but these appear to correlate well with current initiatives seeking to address the risks of nanotechnology. Of particular importance is the "Immediate" section of our gradual pyramid. If it is true, as suggested above, that nanotechnology may be sliding towards stigmatization, producing more complete information about current research, manufacturing and other applications, and about the actual risks and benefits of nanotechnology, is essential to avoid stigmatization and help form appropriate affective reactions to this emerging technology.

Information Gathering and Dissemination

In the immediate future, the greatest need for "regulation" is to increase the accumulation and dissemination of knowledge about the current state of nanotechnology research, development, and application, and about the risks and benefits of specific products and processes. Information gathering and dissemination are essential to properly assess the risks of nanotechnology and to provide accurate and trustworthy messages to the public. Such information may not overcome all negative affective reactions, but accurate and trustworthy messages should at least avoid any widespread affective antagonism or availability cascades.

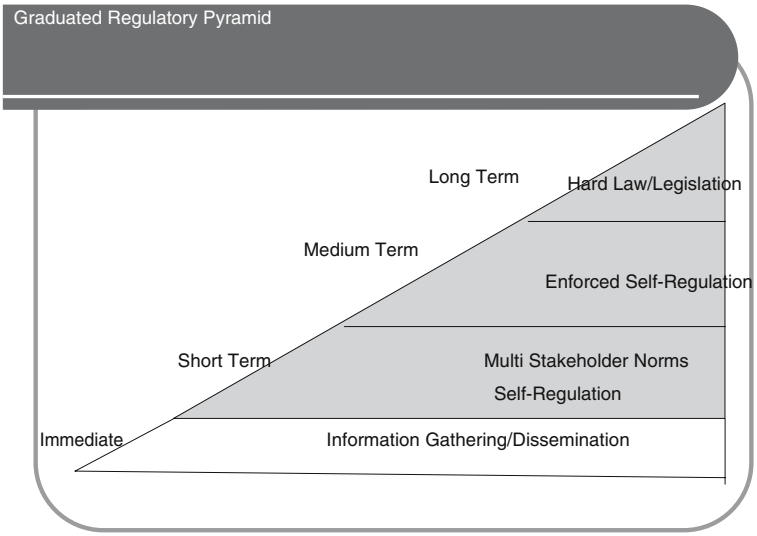

Fig. 3 Building up the regulatory pyramid over time

Numerous nanotechnology stakeholders support this early emphasis on information. For example, the American Chemistry Council (ACC) has adopted a formal *Position on Nanotechnology*. It calls for increased public funding for research into methods to assess the impact of nanotechnology on environment, health, and safety. The ACC also calls for global coordination of regulatory, research and standard-setting activities, including an assessment of the adequacy of existing statutes and regulatory programs that might apply to nanotechnology. The ACC has been joined by an unlikely ally in this effort: Environmental Defense (ED), a non-governmental environmental organization. In a 2005 *Joint Statement of Principles* [15], Environmental Defense and ACC note the urgency to "identify and better understand nanotechnology's potential risks up front." To this end, the two groups call for "an international effort to standardize testing protocols, hazard and exposure assessment approaches, and nomenclature and terminology," as well as a significant increase in public funding for safety research and an assessment of existing regulations. More broadly, the two groups call for a broad "multi-stakeholder dialogue" including all interested parties. In the view of the ACC and ED, such an "open and transparent process" is the best guarantee that the potential risks of nanomaterials will be identified and minimized. We would add that such a process is also the best guarantee of public understanding and trust.

ED has also joined with other partners from industry to seek appropriate regulatory responses to nanotechnology. Perhaps most notably, ED partnered with DuPont to develop a *Nanorisk Framework* [16]. This project aims to develop a practical framework to understand and manage nanotechnology risks. It seeks a responsible approach to development, production, use, and disposal of nanoscale materials across the entire nanotechnology product lifecycle. Like our regulatory model, the project includes several phases. The initial phase includes several steps that are consistent with our approach: (1) identifying the risks of the nanomaterials dealt with by DuPont and identifying the tests appropriate for particular products at various stages of development; (2) developing techniques of risk management, with a focus on safe procedures for handling nanomaterials at different stages of the lifecycle; (3) developing transparency mechanisms, techniques for informing internal and external stakeholders, including the general public, about risk identification and risk management decisions; and finally (4) establishing systems to track the implementation and determine the efficacy of risk management techniques, with appropriate feedback, evaluation, and adjustment. This program seems well designed to produce and disseminate accurate information, develop unconventional forms of "regulation" in the form of safe handling protocols, and build trust among stakeholders and the general public.

Self-Regulation

In the short term, our approach emphasizes self-regulation, coupled with the development of multi-stakeholder norms and policies. Once again, this approach not only recognizes the nascent nature of nanotechnology, but also corresponds to the actions of relevant stakeholders.

The ACC again offers a relevant example. In its *Position on Nanotechnology*, the organization makes clear that, even as other regulatory options are studied, member firms are to apply to their nanotechnology activities the "product stewardship" principles incorporated in the ACC Global Chemicals Management Policy and the Responsible Care program developed by the International Council of Chemical Associations (ICCA) in response to the 1984 Bhopal incident. To be sure, "product stewardship" is a highly amorphous concept, but it incorporates important elements, such as commitments to a product lifecycle approach and to continuous improvement, and represents a familiar self-regulatory approach that business can readily implement. The ICCA has declared that the product stewardship concept will increasingly pervade self-regulatory programs such as Responsible Care, and has pledged to establish a strengthened and unified product stewardship program to evaluate and manage chemical risks and benefits, including those relating to nanotechnology. Meanwhile, the Responsible Care program—which was very weak in its initial form—has been strengthened by the involvement of outside stakeholders through third-party audits of compliance, an approach that should help strengthen public trust in self-regulation within competitive industries. The ACC–ED *Joint Principles* likewise call for "appropriate protective measures" to be implemented as an aspect of responsible technology development while information is gathered and standards created.

The ED–Dupont agreement observes that it would be harmful to business as well as society to commercialize a new technology like nanotechnology before appropriately identifying and managing its risks; potential costs to business might include costly litigation, liability and cleanup requirements. The agreement specifically declares that it is in the best interests of industry, the public, and the environment for business to proactively develop, in advance of government regulation, a framework for responsible nanotechnology management. In addition to directly enhancing safe product development and public acceptance, these actors view a self-regulatory framework as providing a workable model for reasonable government policy at a later time, consistent with our gradual approach to building up a complete regulatory system. In their agreement, DuPont and ED commit to developing both broad self-regulatory principles (e.g., that new nanomaterials will be tested before being marketed) and specific guidelines on implementing those principles. Finally, the partners agree to demonstrate the framework they develop by applying it to an actual product or process; revise and refine the framework following the pilot project; apply the framework across DuPont's activities involving nanotechnology; and disseminate the framework to other firms, industry associations, and government agencies, promoting it as a regulatory model.

Multi-Stakeholder Norms

Ayres & Braithwaite [4] correctly observe that self-regulation alone is unlikely to be satisfactory. Experience with other industries and technologies where firms face strong competitive incentives to minimize self-regulatory expenditures makes clear the need to monitor compliance and exert pressure for compliance on firms, especially in the absence of mandatory regulation; failures of self-regulation can be highly damaging to public confidence, especially if they cause visible harms that influence public attitudes through the action of the availability heuristic. Ayres & Braithwaite conclude that the best way to ensure industry compliance is to bring groups representing the public interest into the regulatory process.

In our incremental regulatory approach, each stage can, and probably should, involve the participation not only of firms, researchers, and other targets of regulation (who may also be engaged in self-regulation), but also of appropriate advocates for the public interest and other stakeholders. Ayers & Braithwaite envisioned a complex formal process for incorporating these groups in public regulatory procedures; especially in the early stages of the gradual regulatory process we envision, however, participation will have to be more informal, as in several recent developments.

The ACC–ED and ED–DuPont agreements already reflect a decentralized multi-stakeholder approach. Moreover, both explicitly endorse broader multi-

stakeholder participation. The ED–DuPont agreement, in particular, commits the parties to "engage a wide range of … stakeholders at various stages throughout the project to draw on their expertise and solicit input…. The project will ... include interim check-points for the Parties to … share interim results with other stakeholders, and solicit input from other stakeholders." In addition, the goal of the ED–DuPont project is to develop a framework for (self-)regulation "that will be accepted, endorsed and adopted by a wide range of stakeholders, including other companies, other public interest groups, academia and government agencies."

The best and most prominent example of a multi-stakeholder approach to voluntary regulation is the Foresight Guidelines for Responsible Nanotechnology Development (Foresight Institute 2006). The Guidelines were sponsored by the Foresight Institute, which was organized explicitly to provide a public forum for discussion of the risks and benefits of nanotechnology and to "pave the way" for its societal acceptance. Institute members include scientists, engineers, business people, investors, ethicists, policy makers and laypersons as well as firms; thus the organization represents a broad spectrum of stakeholders, interests, and opinions. It has been at the forefront of public discussions of nanotechnology risks and benefits.

The Foresight Guidelines (FGL) focus on "productive nanosystems." Currently, these systems form "a research oriented class of nanotechnology that will produce programmable, molecular-scale systems that make other useful nanostructured materials and devices." The Institute sees such systems as qualitatively different from nanomaterials, especially in their regulatory implications.

The FGL were initially developed at an expert workshop held in 1999; they have been revised multiple times through subsequent workshops, web-based community discussion, and other modalities. The version we discuss here is Draft Version 6, released in April 2006.

The FGL make an extraordinarily strong argument for the value of "soft law," especially as applied by researchers and firms themselves. They define soft law broadly, to include ethical behavior, good judgment, "professional guidelines and practices" based in science and knowledge of environmental and ethical issues, "cultural norms" of good practice that pervade scientific research, and professional ethics. According to the FGL, these norms are at least as effective as "hard law" in preventing unsafe practices and promoting action against them. Even in dealing with "rogue" actors who might abuse NT, the FGL suggest that much of the regulatory action can remain at the bottom or in the early stages of the regulatory pyramid. Two examples of soft regulation discussed in the FGL are moral and technical education, and the promotion of safe system designs that make abuse more difficult (in essence, embedding regulation within technology). The FGL include separate guidelines for different groups of actors working with nanotechnology; each guideline is cast as a self-assessment "scorecard," a notably soft form of implementation consistent with the FGL's reliance on ethics and professional norms.

To illustrate the types of norms contained in the FGL, consider the guideline for nanotechnology professionals (basically those involved in R&D). This guideline indicates that researchers should: adopt professional guidelines and ethical practices; engage in proactive stewardship by considering the possible negative consequences of any products subject to research and planning to prevent those consequences or minimize their harmful effects; conceive and develop products using total lifecycle analysis; quickly address any problems that arise; and practice inherently safe system design, avoiding the use of autonomous replicators. Similarly, the guideline for industry calls for proactive self-regulation, tailored to the specific risk profile of individual products and processes; this requires rigorous, balanced analyses of risks and benefits. This guideline also urges the use of inherently safe system design.

Other multi-stakeholder approaches to regulation are being pursued within standard-setting bodies. For example, the ISO established a Technical Committee on nanotechnologies in November 2005. In addition to the basic work of harmonizing terminology, nomenclature, and measurement, the Committee has established a working group, chaired by the USA, to consider "regulatory" standards pertaining to health, safety, and the environment.

Moving Up the Pyramid

In the medium term, as information about nanotechnology risks and benefits is gathered and disseminat-

ed and as society learns from diverse experiments in voluntary self- and multi-stakeholder regulation, it may be necessary to move toward greater governmental involvement, though still short of full-fledged command-and-control regulation, corresponding to the middle levels of the regulatory pyramid. This area of regulatory techniques is highly diverse, and it would be fruitless to speculate on the forms of government involvement that might be established. We briefly discuss one current example of government activity that captures the flexibility and public-private interchange that characterize this area of the pyramid.

Late in 2005, the US Environmental Protection Agency (EPA) launched a "collaborative" project to develop a Nanoscale Materials Stewardship Program. The EPA noted that it has statutory authority under the Toxic Substances Control Act to regulate many nanomaterials as "chemical substances," and that it would continue to implement that authority. Yet it sees the Stewardship Program as a valuable complement to its more traditional regulatory actions. The EPA invited broad stakeholder participation, and intends both to develop and to implement the program collaboratively and with public input.

Some potential components relate to the immediate need for better information about risks and benefits: EPA suggests that it may use the program to compile existing information from researchers and industry, and to encourage the development of testing procedures to produce additional information. More notably, EPA suggests that it may identify and encourage use of a basic set of risk management practices for R&D and commercial applications. To identify such practices, EPA will almost certainly rely on the existing experiments in product stewardship discussed here, such as the ED–DuPont agreement. Once EPA identifies and encourages use of those practices, they will no longer constitute pure self-regulation, but will remain soft law, complementing and to a considerable extent substituting for traditional hard regulation.

Building Up a Pyramid

The EPA Nanomaterials Stewardship Program reflects precisely the approach we espouse here: begin with information gathering and assessment, encourage experiments with self-regulation and multi-stakeholder norms, move gradually to greater governmental involvement to standardize, scale up and supervise voluntary programs, perform all these steps with high levels of transparency and participation, and over time build up to a regulatory end state that retains the best of these voluntary mechanisms at the base of the pyramid, along with formal regulation at the peak of the pyramid, as required.

For a valuable perspective on this approach, consider the actions the FGL suggest for regulators. Many of these guidelines speak to formal, mandatory regulation at the peak of the pyramid: for example, they call for regulators to be granted specific responsibilities and authorities, and for governments to designate a single regulatory entity to coordinate nanotechnology activities across agencies. More strikingly, however, the FGL devote considerable attention to voluntary actions at the base or in the early stages of the pyramid, and to relatively subtle interactions between regulators and the regulated, in the middle levels of the pyramid. For example, the FGL suggest that governments should:

a. Rely not only on "regulations," but also on "consensus standards promulgated by researchers, industry, or government." Whatever their source, regulatory norms should provide clear and specific guidelines and require the use of inherently safe systems.
b. Provide incentives for collaboration among firms, public interest groups and government on mechanisms for continuous improvement and the application of best practices in the handling of nanotechnology. This is a clear endorsement of the product stewardship approach.
c. Provide disincentives for those that fail to follow reasonable principles and guidelines. For example, such actors might be disadvantaged with regard to access to funding, designs, advanced nanotechnology capabilities cooperative market relationships, or collaborative relationships with public interest groups.
d. Enlist public interest groups and other actors in the international community to help prevent deliberate misuse through external verification.

Clearly, then, the FGL envision a regulatory pyramid, with the enforcement of existing and new laws through civil and criminal liability forming only the peak, called into action when lower-level measures prove to be insufficient. In our view, a similar

approach applied over time would serve well both this technology and the interests of the public.

Implementing the Pyramid

A final question, of course, is how our incremental model—which in its early stages relies on decentralized measures taken by a range of private and public actors, including self-regulation and the development of multi-stakeholder norms and policies—can be adopted and implemented by the relevant decision makers. To begin, the preceding discussion has identified numerous spontaneous self-regulatory initiatives and multi-stakeholder programs that seek to identify and address the risks of nanotechnology. Civil society organizations continue to pressure researchers and business firms to act responsibly. Governments support research on nanotechnology impacts and risks, although most observers agree that more could be done. In short, our near-term approach is already being implemented, at least to a considerable degree.

Pure bottom-up initiatives are not, however, the only ways our approach can be implemented. In the near term, public authorities can signal concern that the risks of nanotechnology be adequately identified and addressed; such actions reinforce civil society pressure and remind researchers and industry that the state can intervene with mandatory regulation and a tit-for-tat strategy if necessary. Public authorities can also promote and support private initiatives and steer them in desirable directions, through means such as persuasion, financial incentives, publicity, and the implicit threat of regulation. Indeed, a few of our examples already reflect conscious action by government agencies or public officials; the EPA stewardship program is but one. Over time, of course, the role of public regulation will gradually increase.

In some areas more formal state involvement may be desirable even in the near term. For example, we have previously noted the need for transnational coordination of nanotechnology regulation [1] and urged a multilateral response [42]. One approach might be a "framework convention," adopted by states like any treaty. A framework convention could incorporate the kinds of near- and mid-term approaches we propose here: committing states to support research on the risks of nanotechnology, promote self-regulatory and multi-stakeholder initiatives, encourage and practice transparency and participation, exchange information and experiences, and consult on the form and transnational effects of any proposal for mandatory regulation [1]. Yet the "official" nature of a framework convention would be an important element in achieving cooperation among diverse and competitive states.

In general, however, formal authorization for an incremental approach will not be necessary. The approach may arise through spontaneous actions by researchers, industry and stakeholders, civil society pressure, government support and steering, or even formal government action. It is the incremental approach itself that is important, as we believe it is best suited to address the concerns identified in this paper, and ultimately to build an appropriate and effective regulatory system for the dynamic field of nanotechnology.

Conclusion

Nanotechnology presents enormous challenges to risk management, and existing risk models (including the new precautionary principle) will not be up to the challenge. A more incremental, multi-actor, and multi-component oversight model is needed for nanotechnology. The successful development of such a new risk management approach would not only facilitate the responsible development of nanotechnology, but will create a new precedent that could be used for other emerging technologies of the future. For example, looking to the recent past, a model similar to that proposed here might have helped smooth the introduction of genetically modified foods. As we look to other technology revolutions looming in the future, including emerging developments in telecommunication technologies, surveillance technologies, genetic enhancement, cognitive sciences, and many others, the need to develop new, better models for risk management (starting with nanotechnology) becomes all the more urgent.

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GENETIC SUSCEPTIBILITY AND BIOMARKERS IN TOXIC INJURY LITIGATION

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Abstract: *The tort system generally treats plaintiffs as indistinguishable black boxes, entitled to compensation when a defendant's wrongful act or defective product causes some manifest disease or injury. This current paradigm is likely to change dramatically with recent advances in genetic and related technologies. These new technologies will permit differentiation of individuals with respect to susceptibility and predispositions, and to peer inside the individual plaintiff to identify cellular and molecular markers that identify both the status and etiology of pre-symptomatic disease processes. This Article surveys potential, and in some cases existing, uses of such biomarkers in toxic injury litigation, and assesses the doctrinal, procedural, policy and normative issues presented by these biomarker applications.*

A toxic injury case in the near future might look something like the following. Plaintiff alleges that defendant's product caused her breast cancer. Epidemiology data show that defendant's product may cause a slight increase in breast cancer risk, but the available data are insufficient to establish that the product was more likely than not the cause of plaintiff's cancer. This particular plaintiff, however, has a genetic polymorphism that puts her at an increased susceptibility for cancer from defendant's product, and which allows her to overcome the more likely than not standard. Moreover, a sample of plaintiff's DNA from a blood test performed ten years earlier, before she used defendant's product, shows that she has incurred genetic changes in the interim that exhibit a mutational fingerprint specific to defendant's product. Medical tests also show that her white blood cells contain other biological changes that provide quantitative proof of her exposure to defendant's product.

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But defendant may be able to use similar technologies to buttress its defense. The genetic tests performed on plaintiff may indicate that she is genetically susceptible to many other potentially carcinogenic substances in addition to defendant's product, and any one of those products could have caused her cancer. Further, plaintiff's blood cells may contain biomarkers specific to some of those other agents, proving that plaintiff had indeed been exposed to those substances. Genetic testing may also reveal that plaintiff carries the BRCA1 gene, which puts her at a greatly increased risk of developing breast cancer.[1] Defendant could argue that this genetic predisposition, not defendant's product, caused plaintiff's breast cancer. Alternatively, defendant could argue that even if its product caused or contributed to plaintiff's breast cancer, she would have eventually developed breast cancer even without such exposure because of her genetic predisposition, and therefore the damages for which defendant is liable should be discounted accordingly. Finally, defendant may offer an affirmative defense that its product was not defective, and perhaps did not even require a warning, when its only adverse effect is an unforeseen idiosyncratic response in a genetically susceptible individual.

These types of claims and defenses based on genetic and other biological markers will soon be, and in some cases already are being, applied in toxic injury litigation. To date, most scholarly and popular attention to predictive genetic testing has focused on the potential medical applications of genetic information.[2] Genetic information will, however, have many uses outside the strictly medical context. Already, DNA testing has been used extensively in, and has largely transformed, proof of paternity.[3]

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[1] *See* Patricia Kahn, *Coming to Grips with Genes and Risk*, 274 SCIENCE 496 (1996).

[2] *But see* Mark A. Rothstein, *The Use of Genetic Information for Nonmedical Purposes*, 9 J. L. & HEALTH 109 (1995).

[3] *See* MCCORMICK ON EVIDENCE (5th ed. 1999), at 755-56.

Likewise, DNA forensic testing has established an impressive track record in criminal cases, both in helping to convict the guilty and exonerate the innocent.[4] Although such applications of DNA testing had a tangled scientific and legal genealogy, they are today well accepted and in widespread use.[5] Genetic evidence is likewise likely to transform toxic injury litigation.[6] Although different (and likely more complex and diverse scientific and legal issues will be presented than in the criminal context, genetic testing also has the potential both to help injured victims recover damages from culpable defendants as well as to assist innocent defendants in defending against spurious or unfounded claims of injury. While this type of evidence has much promise for the tort system and its participants, it will also create numerous doctrinal, procedural and normative challenges.

The objective of this Article is to identify the various ways that genetic tests and biomarkers may be used in litigation involving toxic substances, and to evaluate the potential promise and pitfalls of these various applications. Section I briefly summarizes the progress that has been made in identifying and

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[4]*See, e.g.,* Edward Connors, Thomas Lundregan, Neal Miller & Tom McEwen, Convicted by Juries, Exonerated by Science: Case Studies in The Use of DNA Evidence to Establish Innocence After Trial (National Institute of Justice, 1996); 1 MODERN SCIENTIFIC EVIDENCE: THE LAW AND SCIENCE OF EXPERT TESTIMONY sec. 15 (David L. Faigman et al. eds., 1997).

[5]*See* MCCORMICK ON EVIDENCE (5th ed. 1999), at 759-62.

[6]*See* Mark S. Ellinger, *DNA Diagnostic Technology: Probing the Problem of Causation in Toxic Torts*, 3 HARV. J. LAW & TECH. 31 (1990); Bob Van Voris, *Tort Lawyers Discover the Power of Genetics*, NAT'L L.J., Sept. 14, 1998, at A1; Wendy Yap & David Rejeski, *Environmental Policy in the Age of Genetics*, ISSUES IN SCI. & TECH., Fall 1998, at 33, 35; Anthony P. Decaprio, *Biomarkers: Coming of Age for Environmental Health and Risk Assessment*, 31 ENVTL. SCI. & TECH. 1837, 1842 (1997); Ralph H. Johnson, *Biological Markers in Tort Litigation*, 1988 STAT. SCI. 367, 370 (1988); NICHOLAS A. ASHFORD, CHRISTINE J. SPADAFOR, DALE B. HATTIS & CHARLES C. CALDART, MONITORING THE WORKER FOR EXPOSURE AND DISEASE: SCIENTIFIC, LEGAL, AND ETHICAL CONSIDERATIONS IN THE USE OF BIOMARKERS 156-158 (1990); Allen Kanner, *Emerging Conceptions of Latent Personal Injuries in Toxic Tort Litigation*, 18 Rutgers L. J. 343, 350 (1987).

validating biomarkers of susceptibility, effect and exposure. Section II inventories and analyzes various ways in which such biomarkers could be, and in some cases have been, used in toxic injury litigation. Finally, Section III addresses some of the policy and normative issues raised by the inevitable widespread use of biomarkers in litigation.

I. BIOMARKERS OF GENETIC SUSCEPTIBILITY, EFFECTS AND EXPOSURE

Toxicology, the science of evaluating the effects of toxic substances on the body, has traditionally focused on exposure and disease, with everything between remaining a black box.[7] Yet, a cascade of events occurs between ambient exposure and the development of manifest disease, including intake of the substance into the body, transfer to the target site where the initial interaction occurs, metabolism into derivative compounds that are often the active toxicant, development of early biological effects, progression into more significant effects such as altered tissue or cell structure and function, and finally manifestation of clinical disease, such as a tumor.[8] Previously, little information was available to identify and characterize these intermediate events or to evaluate directly the influence of other intrinsic and extrinsic factors on these stages of disease development.[9]

"Biomarkers" provide diagnostic information about what happens in the black box between exposure and disease.[10] A biomarker is defined as "any measurement in or from biological material that

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[7]*See* V.K. Bhatnagar & G. Talaska, *Carcinogen Exposure and Effect Biomarkers*, 108 TOXICOLOGY LETTERS 107,108 (1999); Decaprio, *supra* note 6, at 1837.

[8]Decaprio, *supra* note 6, at 1838.

[9]Decaprio, *supra* note 6, at 1838.

[10]Bhatnagar & Talaska, *supra* note 7, at 108; Decaprio, *supra* note6, at 1838..

defines an exposure or response to that exposure."[11] Typically, biomarkers are classified into three broad categories measuring (i) susceptibility, (ii) effect, or (iii) exposure.[12] A critical feature of all three types of biomarkers is that they provide important information about a specific individual rather than the population as a whole.

Over the past two decades, tremendous progress has been made in the theoretical understanding and practical application of all three categories of biomarkers. Some of the biomarkers in each category are based on genetic changes, and much of the recent progress and interest in biomarkers can be attributed to technical advances in molecular genetic techniques.[13] Included among these is the Human Genome Project, which is preparing a complete sequencing map of the human genome, which will generate an almost unlimited number of genetic markers.[14] Also critical to progress in this area is the development of DNA microarrays, sometimes referred to as "gene chips," that can be used to quickly and cheaply screen tissue samples for thousands of genetic markers simultaneously.[15]

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[11] Andrij Holian, *Air Toxics: Biomarkers in Environmental Applications - Overview and Summary of Recommendations*, 104 ENVTL. HEALTH PERSPECT. 851 (1996).

[12] National Research Council (NRC), *Biological Markers in Environmental Health Research*, 74 ENVTL. HEALTH PERSPECT. 3, 3 (1987). There is a continuum between biomarkers of exposure and effect. *Id.*; Decaprio, *supra* note 6, at 1838.

[13] *See* Decaprio, *supra* note 6, at 1837.

[14] The Human Genome Project is described at http://www.ornl.gov/hgmis/home.html.

[15] *See* J.C. Rockett and D.J. Dix, *Application of DNA Arrays to Toxicology,* 107 ENVTL. HEALTH PERSPECT. 681 (1999). According to one account, "Microprocessors have reshaped our economy, spawned vast fortunes and changed the way we live. Gene chips could be even bigger." David Stipp, *Gene Chip Breakthrough*, FORTUNE, March 31, 1997, at 56.

A. Biomarkers of Susceptibility

Biomarkers of susceptibility reveal an individual's increased (or possibly decreased) susceptibility to an environmental exposure, often as a result of genetic predisposition.[16] The Environmental Genome Project ("EGP"), established by the National Institute of Environmental Health Sciences ("NIEHS"), is intended to identify and study common genetic variants that may be associated with differential responses to environmental exposures.[17] For example, recent findings indicate that some common genetic polymorphisms play a major role in human cancer susceptibility.[18]

Many of the most important genetic polymorphisms influence the metabolism of toxic substances. The body generally breaks down and eventually eliminates toxic chemicals in two stages. In the first stage, mediated by "Phase 1" enzymes such as the cytochrome p450 enzyme complex, the toxic chemical is oxidized to form a series of intermediates.[19] These metabolites are often highly reactive, and

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[16] Other sources of susceptibility in addition to genetics include ethnicity, age, gender, preexisting medical impairments, and nutritional status. *See* Frederica P. Perera, *Environment and Cancer: Who Are Susceptible?*, 278 SCIENCE 1068, 1070-72 (1997).

[17] *See* [cite Sharp, this issue]; Jocelyn Kaiser, *Environment Institute Lays Plan for Gene Hunt*, 278 SCIENCE 569 (1997). The website for the EGP is http://www.niehs.nih.gov/envgenom.

[18] *See* Perera, *supra* note 16, at 1069-70; John A. Timbrell, *Biomarkers in Toxicology*, 129 TOXICOLOGY 1, 10-11 (1998); J. A. Indulski & W. Lutz, *Metabolic Genotype in Relation to Individual Susceptibility to Environmental Carcinogens*, 73 INT ARCH OCCUP ENVIRON HEALTH 71 (2000); Edward J. Calabrese, *Biochemical Individuality: The Next Generation*, 24 REG. TOXICOL. PHARMACOL. S58 (1996); Dale Hattis & Sue Swedis, *Uses of Biomarkers for Genetic Susceptibility and Exposure in the Regulatory Context*, __ JURIMETRICS __ (this issue). A genetic "polymorphism" is generally defined as a genetic variant that is present in at least one percent of the human population. *See* Wolfgang Sadée, *Pharmacogenomics*, 319 BR. MED. J. 1, 2 (1999).

[19] Matti Lang & Olavi Pelkonen, *Metabolism of Xenobiotics and Chemical Carcinogenesis*, in METABOLIC POLYMORPHISMS AND SUSCEPTIBILITY TO CANCER (eds. P. Vineis, et al., 1999), at 13, 13.

can produce mutations, cancer, or other toxicological endpoints.[20] Numerous polymorphisms of the cytochrome p450 genes have been identified that can affect the formation of reactive intermediates. For example, about 10 percent of the Caucasian population carries a variant of one cytochrome p450 gene (*CYP1A1*) that increases the rate of phase I reactions, thereby increasing the formation of reactive metabolites, and which has been associated with increased lung cancer risk in smokers in some (but not all) studies.[21] In another example of both medical and legal significance, the popular allergy drug Seldane was withdrawn from the market when it was found, when taken with certain other drugs such as erythromycin, to cause potentially fatal heart problems in people with a mutation in another p450 gene.[22]

In contrast, the phase II enzymes - such as glutathione s-transferase ("GST") and N-acetyltransferase ("NAT") - generally function to detoxify the reactive metabolites formed by phase I enzymatic reactions.[23] Common polymorphisms of toxicological significance have also been identified for the genes coding for these enzymes. In approximately fifty percent of the Caucasian population, one of the genes (*GSTM1*) coding for the GST enzymes is completely deleted, which is associated with an increased risk of bladder and lung cancer from exposure to several important toxic substances normally detoxified

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[20] *Id.*

[21] *See* Perera, *supra* note 16, at 1070; Indulski & Lutz, *supra* note 18, at 72-74.

[22] *See* Manish Bhandari, Rajesh Garg, Robert Glassman, Philip C. Ma & Rodney W. Zemmel, *A Genetic Revolution in Health Care*, McKinsey Quart., Sept. 22, 1999, at 58; David Brown, *P450: Enzymes with the Answers on Drug Risks*, Wash. Post, April 10, 2000, at A9.

[23] *See* Lang & Pelkonen, *supra* note 19, at 17-19.

by the GSTM1 enzyme.[24]

These and other genetic polymorphisms are important because they are found in significant proportions of the population and can result in a several-fold increase in risk of cancer and other adverse effects from toxic exposures.[25] Nevertheless, several factors complicate their practical application. For one thing, the results of various studies for particular genetic polymorphisms are often contradictory, with increased susceptibility to toxic substances found in some populations but not others.[26] It may be that other environmental, genetic and physiological factors cause these variations. Various susceptibility genes also interact with each other, further complicating efforts to predict individual susceptibility.[27] Many genetic susceptibilities also have varying effects at different concentrations of a toxic substance, in many cases being more important at low exposures.[28] Notwithstanding these limitations, genetic markers of susceptibility demonstrate that there is substantial inter-individual differences in risks to toxic substances, and will increasingly be capable of identifying susceptible individuals.

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[24]Radim J. Sram, *Effect of Glutathione S-transferase M1 Polymorphisms on Biomarkers of Exposure and Effects*, 106 ENVTL. HEALTH PERSPECT. 231 (1998); Perera, *supra* note 16, at 1070; Indulski & Lutz, *supra* note 18, at 77-79.

[25]Other common genetic polymorphisms also appear to play a significant role in susceptibility to toxic substances, including mutations of the genes involved in DNA repair. *See* Paolo Vineis, Angelo d'Errico, Nuria Malats & Paolo Boffetta, *Overall Evaluation and Research Perspectives*, METABOLIC POLYMORPHISMS AND SUSCEPTIBILITY TO CANCER (eds. P. Vineis, et al., 1999), at 403.

[26]*See* Ari Hiroven, *Genetic Factors in Individual Responses to Environmental Exposures,* 37 J. OCCUP. & ENVTL. MED. 37 (1995).

[27]*See* Perera, *supra* note 16, at 1070.

[28]*See* Calabrese, *supra* note 18, at S62, S65 (1996); Perera, *supra* note 16, at 1070.

B. Biomarkers of Effect

Biomarkers of effect measure bodily changes that are quantitatively or qualitatively predictive of health impairment resulting from toxic exposures.[29] Biomarkers of effect are useful for identifying symptomatic or pre-symptomatic persons who have been adversely affected by a toxic exposure, as well as to evaluate disease progression and estimate the risk of future disease. Some of the most promising biomarkers of effect are adducts, in which a toxic substance or its metabolites binds with DNA or proteins to form a stable and characteristic chemical complex.[30] The formation of DNA adducts is believed to be an initial step in the mutation process, although not all adducts necessarily result in mutation.[31] Several hundred different carcinogen-DNA adducts have been identified to date, with many carcinogens forming distinct patterns of adducts with respect to type and location on the DNA macromolecule.[32]

Despite their current utility and even greater future promise, DNA adducts have several important limitations. First, because it is difficult to sample DNA adducts in many critical tissues in which disease is likely to arise, such as the lung or liver, most sampling is conducted using more accessible

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[29]Decaprio, *supra* note 6, at 1839.

[30]Bhatnagar & Talaska, *supra* note 7, at 108.

[31]*Id.* at 110-111; Mortimer L. Mendelsohn, *The Current Applicability of Large Scale Biomarker Programs to Monitor Cleanup Workers,* in BIOMARKERS AND OCCUPATIONAL HEALTH: PROGRESS AND PERSPECTIVES (eds. M. Mendelsohn, J. Peeters & M.J. Normandy, 1995), at 9, 15.

[32]Christopher P. Wild & Paola Pisani, *Carcinogen DNA and Protein Adducts as Biomarkers of Human Exposure in Environmental Cancer Epidemiology*, 22 CANCER DETECTION & PREVENTION 273, 276-77 (1998). DNA adducts can be detected at levels as low as one DNA adduct per cell. *See* Timbrell, *supra* note 18, at 11.

surrogate tissues such as blood cells or urine, which may not be representative of the target tissue.[33] Second, there appears to be significantly different inter-individual rates of adduct formation, likely due to genetic differences in metabolism or other causes.[34] Third, many (but not all) DNA adducts have relatively short durations, lasting only from minutes to several months depending on the marker involved, and therefore measurements of adduct levels may only be relevant if taken within an appropriate time after exposure.[35]

Other biomarkers of effect include various types of chromosomal aberrations, metabolic changes such as enzyme induction or inhibition, increased cell proliferation in tissues (hyperplasia), and functional test abnormalities.[36] Monitoring for genetic mutations in exposed individuals can also provide useful biomarkers of effect, and several "reporter gene" assays have been developed to monitor mutational rates in blood cells.[37] Even more specific and informative assays are made possible by recent findings that several important human carcinogens each induce their own characteristic "mutational fingerprints" at precise

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[33]Bhatnagar & Talaska, *supra* note 7, at 111. *But see* Michael S. Kopreski, et al., *Somatic Mutation Screening: Identification of Individuals Harboring K-ras Mutations With the Use of Plasma DNA,* 92 J. NAT'L CANCER INST. 918 (2000) (oncogene mutations found in blood plasma extracellular DNA are a biomarker of colorectal neoplasms with same mutation). Significant progress is also being made in monitoring for biomarkers in other accessible tissues that may be more relevant to certain disease processes. *See* Salama A. Salama, Milagros Serrana and William W. Au, *Biomonitoring Using Accessible Human Cells for Exposure and Health Risk Assessment*, 436 MUTATION RES. 99 (1999).

[34]Wild & Pisani, *supra* note 32, at 278-79. *But see* Bhatnagar & Talaska, *supra* note 7, at 109-112 (finding no impact of metabolic differences on formation of certain biomarkers).

[35]Mendelsohn, *supra* note 31, at 15; Wild & Pisani, *supra* note 32, at 278.

[36]*See* Decaprio, *supra* note 6, at 1840.

[37]Hattis & Swedis, *supra* note 18, at __ [this volume].

sites in specific genes, such as the important tumor suppressor gene *p53*.[38] Thus, the detection of a characteristic genetic change might indicate the initiation of the cancer process, as well as the specific cause of that event.

C. Biomarkers of Exposure

Biomarkers of exposure provide a qualitative or quantitative measure of an individual's exposure to a particular agent. Exposure biomarkers measure the concentration of the substance within the body (i.e., internal dose), which provides a more accurate and useful estimate of exposure than the concentration of the substance in the ambient air or exposure vehicle (*e.g.,* food, water, or product), which has traditionally been used for exposure analysis.[39] A critical characteristic of biomarkers of exposure is their duration, as many biomarkers only measure recent exposures.[40] The most straightforward exposure marker is the presence of the toxic agent or its metabolites in the human body. The length of time in which such agents remain in the body varies considerably depending on the substance involved.[41] DNA and protein

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[38]Curtis C. Harris, *p53: At the Crossroads of Molecular Carcinogenesis and Risk Assessment*, 262 SCIENCE 1980 (1993); Steven J. Smith *et al.*, *Molecular Epidemiology of p53 Protein Mutations in Workers Exposed to Vinyl Chloride*, 147 AM. J. EPIDEMIOL. 302 (1998); Ian C. Semenza & Lisa H. Weasel, *Molecular Epidemiology in Environmental Health: The Potential of Tumor Suppressor Gene p53 as a Biomarker*, 105 (Suppl. 1) ENVTL HEALTH PERSPECT. 155, 155-56 (1997); Hattis & Swedis, *supra* note 18, at __ [this volume]. The p53 gene plays a critical role in controlling cell division, and mutated p53 genes are found in half of all human tumors. *See* Harris, *supra*, at 1980; Semenza & Weasel, *supra*, at 156.

[39]Decaprio, *supra* note 6, at 1839 (body intake affected by numerous factors such as route of exposure, physiological characteristics of the body, chemical characteristics of the substance).

[40]*See* Hattis & Swedis, *supra* note 18, at __ [this volume].

[41]*Id.* at __ [this volume].

adducts can also provide an accurate molecular dosimeter of exposure.[42] Adducts have the added benefit of being able to measure extremely low levels of exposure which would previously go undetected.[43]

D. Current Status of Biomarkers

Before it can have practical application, a biomarker must be adequately characterized and validated to establish that it accurately and consistently measures exposure or predicts disease.[44] A large number of potential biomarkers have been identified and are at various stages in their development and validation. Most of these biomarkers are not yet ready for practical application, although some have been validated and are in current use.[45] Many complications remain, especially in accounting for such factors as intra- and inter-individual variations in biomarker responses, interactions between different biomarkers or susceptibilities, variations in biomarker response over ranges of exposures, and correlating human and animal

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[42]*See* Bhatnagar & Talaska, *supra* note 7, at 110-11; Decaprio, *supra* note 6, at 1840; Herman A. Schut & Kathleen T. Shiverick, *DNA Adducts in Humans as Dosimeters of Exposure to Environmental, Occupational, or Dietary Genotoxins*, 6 FASEB J 2942 (1992).

[43]*See* Paul A. Schulte, *Contribution of Biological Markers to Occupational Health*, 20 AM. J. IND. MED. 435, 436 (1991) (noting that biomarkers can increase sensitivity in detecting exposures by a factor of one billion, but cautioning that "our ability to measure out-strips our ability to interpret what is measured.").

[44]NRC, *supra* note 12, at 6-7; Jonathan B. Ward & Rogene E. Henderson, *Identification of Needs in Biomarker Research*, 104 (Supp. 5) ENVTL. HEALTH PERSPECT. 895, 898 (1996); John D. Groopman & Thomas W. Kensler, *The Light at the End of the Tunnel for Chemical-Specific Biomarkers: Daylight or Headlight?*, 20 CARCINOGENESIS 1-4 (1999); DeCaprio, *supra* note 6, at 1840.

[45]*See* Vineis *et al.*, *supra* note 25, at 407; A. Aitio & A. Kallio, *Exposure and Effect Monitoring: A Critical Appraisal of Their Practical Application*, 108 TOXICOL. LET. 137 (1999); Schulte, *supra* note 43, at 444; Marvin S. Legator, *Application of Biomarkers: Getting Our Priorities Straight*, in BIOMARKERS AND OCCUPATIONAL HEALTH: PROGRESS AND PERSPECTIVES (eds. M. Mendelsohn et al., 1995), at 61, 67 (existing biomarker applications in chemical industry "demonstrate the feasibility of detecting low-level chronic exposure by currently available genetic monitoring techniques.").

biomarker responses.[46] Yet, despite these challenges, rapid progress is being made in the development and validation of biomarkers, and this new technology is already beginning to transform our understanding of, and strategies to address, toxic effects.[47]

II. POTENTIAL USES OF BIOMARKERS IN TOXIC INJURY LITIGATION

There are many possible applications of biomarkers in toxic injury litigation, but to date little legal analysis of these potential applications.[48] This section identifies and briefly evaluates many of those potential applications, grouped into categories based on whether they are used to (a) establish a new cause of action or defense, (b) demonstrate causation or lack thereof, or (c) determine the amount of damages if liability exists. Creative trial lawyers will undoubtedly conceive additional legal applications of biomarkers beyond those considered here.

One preliminary point should be emphasized at the outset. In addition to the various potential direct applications of biomarkers in tort litigation discussed below, perhaps the greatest contribution of biomarkers to such litigation will come from the revolution they are bringing about in predictive toxicology.

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[46]*See* Frederica Perera, *The Potential Usefulness of Biological Markers in Risk Assessment*, 76 ENVTL. HEALTH PERSPECT. 141, 143-44 (1987); Ward & Henderson, *supra* note 44, at 896-99.

[47]Groopman & Kensler, *supra* note 44, at 8 ("Biomarker strategies measuring exposure in individuals could completely change how environmental regulations are established...."); Ward & Henderson, *supra* note 44, at 899; Decaprio, *supra* note 6, at 1846; A. Dan Tarlock, *Genetic Susceptibility and Environmental Risk Assessment: An Emerging Link*, 30 Envtl. L. Rev. 10277 (2000) (discussing implications of genetic susceptibility findings for environmental regulation).

[48]Decaprio, *supra* note 6, at 1842 ("To date, little discussion of the potential uses of biomarkers in the courtroom have appeared in the legal/scientific literature. This can be expected to change as more biomarkers undergo validation and the legal community becomes more aware of their advantages."). *But see* Ellinger, *supra* note 6; Susan R. Poulter, *Genetic Testing in Toxic Injury Litigation: The Path to Scientific Certainty or Blind Alley?*, __ JURIMETRICS __ (this issue).

For example, the use of genetic markers and gene microarrays has spawned the new field of toxicogenomics, which studies the impact of potentially toxic compounds on the expression of genes.[49] These new techniques will result in more rapid screens for toxicity, which is critical given the thousands of commercial substances for which inadequate toxicity data are available.[50] In addition to identifying toxic compounds, these techniques will also greatly expand understanding of the mechanism of toxicity for many toxic substances, resulting in more realistic risk estimates.[51] This influx of new toxicological data will undoubtedly benefit future toxic tort litigants.[52]

A. Cause of Action or Defense

1. Duty to Warn of Susceptibility

A product manufacturer has a duty to warn of adverse effects of its products, which may

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[49]*See* E.F. Nuwaysir, M. Bittner, J. Trent, J.C. Barrett, C.A. Afshari, *Microarrays and Toxicology: The Advent of Toxicogenetics*, 24 MOLECULAR CARCINOGENESIS 153 (1999); William D. Pennie, Jonathan D. Tugwood, Gerry J.A. Oliver & Ian Kimber, *The Principles and Practices of Toxicogenomics: Applications and Opportunities*, 54 TOXICOL. SCI. 277 (2000); Jennifer F. Medlin, *Timely Toxicology*, 107 ENVTL. HEALTH PERSPECT. A256 (1999); Rockett & Dix, *supra* note 15, at 681-85.

[50]For example, the NIEHS has developed a "ToxChip," which is a DNA microarray that permits the simultaneous monitoring in cells of the expression of several thousand genes relevant to toxicological response, thus producing a toxicant "signature" that can be used to characterize and categorize toxic agents by their mode of action. NIEHS, Press Release: Environmental Health Inst. to Use Gene Chips to Evaluate Chemicals for Potential Harm to Humans (Feb. 29, 2000) (available at http://www.niehs.nih.gov/oc/news/toxchip.htm); *see also* Medlin, *supra* note 49, at A256-57.

[51]*See* Pennie *et al.*, *supra* note 49, at 277; Margie Patlak, Unraveling Cancer Risk with Cellular and Molecular Tools, ENVTL. SCI. & TECH., July 1, 1998, at 312A, 313A-15A.

[52]*See, e.g.,* Friends of the Earth (UK), *Crisis in Chemicals* 41-42 (2000) (discovery of and screening for individual genetic susceptibilities will substantially increase the chances of successful legal brought by those injured by toxic exposures); Charles Arthur, *Gene Project "Will Unleash Lawsuits,"* THE INDEPENDENT (U.K.), June 5, 2000, at (reporting Friends of Earth study).

include the duty to disclose available information on the existence and means of identifying individuals who are genetically susceptible to a product.[53] As genetic susceptibilities to particular products or substances are identified, and as genetic tests for these susceptibilities become commercially available, susceptible individuals injured by the product could thus bring claims contending that a manufacturer failed to warn of the potential genetic susceptibility to the product.[54]

Similarly, a worker who is genetically susceptibility to a workplace exposure might claim that his employer,[55] or the manufacturer of a hazardous material used in the workplace, was liable for failing to conduct or recommend genetic susceptibility testing of the worker.[56] In addition to a potential legal duty to make genetic susceptibility testing available to an employee, an employer conceivably could have a duty

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[53]*E.g.,* Restatement (Second) of Torts, § 402(j) (requiring warnings to susceptible individuals); *Woodbury v. Janssen Pharmaceutica, inc.*, 1997 WL 201571,* 8-10, No. 93 C 7118 (N.D. Ill. 1997) (denying summary judgment to drug manufacturer on claims that product warnings did not warn about increased risk to susceptible subgroups). *See also infra* notes 75-87 and accompanying text (elaborating on duty to warn susceptible individuals).

[54]*See also* Sadée, *supra* note 18, at 3 ("Once the genetic component of a severe adverse drug effect is documented, doctors may be obliged to order the genetic test to avoid malpractice litigation.").

[55]While the exclusivity provision of worker compensation laws generally prohibit a worker from suing his employer, some exceptions exist, such as for willful or wanton imposition of risks. To the extent that biomonitoring of employees provides an employer with better information on risks to workers, such information might increase the likelihood of "knowing" imposition of risks that could open the door to more employee lawsuits. *See* Lisa J. Raines, *Biological Testing and Occupational Disease Liability*, 28 J. OCCUP. MED. 921, 923 (1986).

[56]*Id.* An employee could also sue an employer's physician who do not provide sufficient warnings or medical advice based on the results of genetic tests. *See* Katherine Brokaw, *Genetic Screening in the Workplace and Employers' Liability*, 23 COLUM. J. L. & SOC. PROBS. 317, 341-45 (1990).

to exclude susceptible workers from a hazardous workplace in some situations.[57] Reducing worker exposures through engineering controls, personal protective equipment or other means would usually be the preferred approach for preventing hazardous exposures, but in some cases exposure prevention may be infeasible or highly cost-ineffective.[58] While many commentators are critical of genetic testing of employees for susceptibility,[59] an employer could potentially be liable for not testing and excluding genetically susceptible workers from a hazardous workplace if that was the only feasible method to prevent a potentially harmful toxic exposure.[60]

A plaintiff might also argue that a manufacturer or employer failed to adequately test its product for potential effects on susceptible persons. A manufacturer has a duty as part of its obligation to

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[57]*See* Sram, *supra* note 24, at 236 (genetically susceptible workers should be excluded from workplaces where they would be at a substantially increased risk of serious harm).

[58]*See* Lillian Trettin, Catherine Musham & Richard Jablonkia, *Genetic Monitoring in the Workplace: A Tool Not A Solution*, 10 RISK: HEALTH, SAFETY & ENV'T 31, 37 (1999).

[59]*E.g.*, DOROTHY NELKIN & LAURENCE TANCREDI, DANGEROUS DIAGNOSTICS: THE SOCIAL POWER OF BIOLOGICAL INFORMATION (1989); ELAINE DRAPER, RISKY BUSINESS: GENETIC TESTING AND EXCLUSIONARY PRACTICES IN THE HAZARDOUS WORKPLACE (1991). Genetic testing of employees, and the use of that information in making employment decisions, also raises legal issues and potential legal claims under employment and discrimination laws, which are beyond the scope of this paper. *See* Karen Rothenberg *et al.*, *Genetic Information and the Workplace: Legislative Approaches and Policy Challenges*, 275 SCIENCE 1755 (1997); ASHFORD *et al.*, *supra* note 6, at 125-64.

[60]*See* Frances H. Miller, *Biological Monitoring: The Employer's Dilemma*, 9 Am. J. Law & Med. 387, 400 (1984) ("companies failing to screen for genetic defects that increase workers' susceptibility to particular occupational illnesses may fall so far below the industry standard of care as to expose themselves to tort as well as worker's compensation liability."). The related issue of whether a genetically susceptible employee who chooses to work in a hazardous job site would be contributory negligent or have assumed the risk is discussed *infra* at notes 126-130 and accompanying text.

exercise due care to undertake reasonable testing to determine the safety of its product.[61] A plaintiff could argue that a defendant that failed to test its product for its effects on hypersensitive individuals may be liable for lack of due care.[62] Yet, with hundreds of genetic susceptibility genes already identified, or waiting to be identified as a result of the Human Genome Project, a product manufacturer cannot be expected to test its product on every possible variant of human susceptibility. Presumably, there would have to be some reasonable basis for a manufacturer to have known about the likelihood of a potential susceptibility among the intended users of a product before being found liable for failure to test the product for adverse effects on susceptible subgroups.[63]

In one of the first actions of this kind, a plaintiff alleges that the manufacturer of a widely-used vaccine for lyme disease (LYMErix) failed to warn that approximately thirty percent of the population

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[61]*E.g.*, Restatement (Third) of Torts: Products Liability, §2 comment m, at 34 (manufacturer has duty "to perform reasonable testing prior to marketing a product and to discover risks and risk-avoidance measures that such testing would reveal."); Borel v. Fibreboard Paper Products Corp., 493 F.2d 1076, 1090 (5th Cir. 1973), *cert. denied*, 419 U.S. 869 (1974) ("a manufacturer has a duty to test and inspect his product").

[62]Such a claim was advanced in Bingham v. Terminix Intl. Co., 896 F. Supp 642 (S.D.Miss. 1995), where the plaintiff claimed that a home pesticide application company had failed to test the effects of chronic low-level exposures of its pesticide products to "hypersensitive" individuals such as the plaintiff. The court dismissed this claim on the ground that it was closely related to the plaintiff's duty to warn claim, which was preempted by the Federal Insecticide, Fungicide and Rodenticide Act ("FIFRA"). *Id.* at 645 n.7. *See also* Singleton v. Airco, Inc., 80 F.R.D. 467, 468 (S.D. Ga. 1978) (dismissing on jurisdictional grounds plaintiff's claim against drug manufacturers for failure to provide adequate warnings for patients claiming a "genetic susceptibility to hyperthermia").

[63]Up until now, manufacturers which test their products on humans usually generally try to conduct the testing on "normal" or "average" subjects, excluding individuals with known abnormal conditions or predispositions from the study groups. As genetically susceptible conditions become identified and identifiable in individuals, companies may be required to test their products on a broader range of gentotypes.

has a specific genotype (HLA-DR4+) which places them at risk of developing "treatment-resistant Lyme Arthritis" when exposed to the vaccine.[64] The plaintiff contends that the manufacturer should not only have warned about the susceptibility in the population, but should have also warned vaccine users of "the need to be screened for the HLA-DR4 gene" prior to inoculation.[65] The manufacturer and the Food and Drug Administration have denied that the vaccine causes such autoimmune arthritis in susceptible recipients, claiming that an independent medical review board found no evidence of such effects during premarket trials of the vaccine, and that no unusual side effects have been observed in the more than one million Americans who have received the vaccine.[66] Putting aside the disputed factual predicate of this particular litigation, which remains to be resolved by the courts, the suit is a likely harbinger of future cases in which plaintiffs contend that a product manufacturer failed to adequately test its product or warn consumers with respect to adverse effects in genetically susceptible subpopulations.

2. No Defect for Effects on Hypersensitive Individuals.

Conversely, a manufacturer might argue that its product is not defective or unreasonably dangerous if it only harms individuals who harbor a rare genetic susceptibility to the product.[67] The footing

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[64]Cassidy v. SmithKline Beecham Corp., No. 99-10423 , Complaint ¶ 10(PA C.P., Chester Cty., filed Dec. 14, 1999) (copy on file with author) (cited hereinafter as "*Cassidy* Complaint"]. *See Class Action Accuses SKB of Hiding Lymerix Dangers*, ANDREWS PHARM. LITIG. REP., Jan. 2000, at 10.

[65]*Id.* ¶31(f). According to the Complaint, the presence of the specific HLA genotype could be determined using a "simple screening blood test." *Id.* ¶ 19.

[66]*See SmithKline Responds to Lyme Vaccine Class Action*, MEALEY'S EMERGING DRUGS AND DEVICES, Jan. 7, 2000, at 13; Holcomb B. Noble, *3 Suits Say Lyme Vaccine Caused Severe Arthritis*, N.Y. TIMES, June 13, 2000, at D6.

[67]*E.g.*, Josh H. Kardisch & Joseph J. Ortego, *Allergic or Idiosyncratic Reactions as a Products Liability Defense*, FOR THE DEFENSE, Aug. 1994, at 15, 15. This argument is distinct from the defense

for such a defense is provided by cases such as *Cavallo v. Star Enterprise*,[68] in which a home owner claimed to become ill from inhaling fuel vapors resulting from a spill at a nearby petroleum distribution terminal. In denying a right to recovery on her personal injury claim, the Fourth Circuit Court of Appeals held that only those adverse effects that would be suffered by a "normal" person are cognizable, and thus plaintiff's own allegation that she was "highly susceptible" to fuel vapors precluded her recovery.[69]

Two seemingly contradictory doctrines are relevant to this potential genetic susceptibility defense. Weighing against such a defense is the general rule that a defendant takes a plaintiff as it finds her, and thus the unforseen fact that a particular plaintiff was predisposed or susceptible to the injury in question does not relieve the defendant from liability.[70] This rule is known as the "thin skull" or "eggshell skull" doctrine.[71] The rationale for this rule is that a tortfeasor who breaches a duty of care should carry the risk of any unexpected injury resulting from a predisposed or vulnerable victim. The case law under this doctrine holding a negligent defendant responsible for "lighting up" or "activating" a dormant condition or

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that the person's genetic susceptibility, rather than exposure to defendant's product, was the *sole* cause of the injury, which is discussed at *infra* notes 188-203 and accompanying text.

[68]100 F.3d 1150 (4th Cir. 1996).

[69]*Id.* at 1154.

[70]Vosburg v. Putney, 50 N.W. 403 , 404 (Wisc. 1891) ("the rule of damages in actions for torts ... [is] that the wrongdoer is liable for all injuries resulting from the wrongful act, whether they could or could not have been foreseen by him.")

[71]22 Am. Jur. 2d Damages § 281. *See generally* Gary L. Bahr & Bruce N. Graham, *The Thin Skull Plaintiff Concept: Evasive or Persuasive*, 15 LOYALA L. REV. (LA) 409 (1982).

predisposition would appear to apply to the unexpected damages in a genetically susceptible plaintiff.[72]

Indeed, one of the earliest cases applying the "thin skull" doctrine involved a plaintiff who allegedly suffered from a genetic predisposition to dementia inherited from her mother.[73] The plaintiff was a young girl who displayed no symptoms of dementia until she was hit by lumber falling off a passing train. Although she received only superficial physical injuries, she apparently developed full-blown dementia in response to the psychological trauma of the accident. The court appeared to accept the defendant's argument that the plaintiff's dementia was inherited, but it nevertheless held the railroad fully liable for the girl's dementia under the thin skull doctrine. In a frequently quoted passage, the court concluded that "[t]he duty of care and of abstaining from injuring another is due to the weak, the sick, the infirm, equally with the healthy and the strong; and, when that duty is violated, the measure of damage is the injury inflicted, even though that injury might have been aggravated, or might not have happened at all, but for the peculiar physical condition of the person injured."[74]

In other decisions, however, courts have applied a different doctrine that appears contrary to the thin skull doctrine, in which a product that produce an idiosyncratic response in a very small subset

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[72] *See, e.g.,* Schafer v. Hoffman, 831 P.2d 897 (Col. 1992) (en banc) ("The doctrine appropriately applies where a plaintiff may be predisposed or more susceptible to ill effects than a normal person."); Owen v. Dix, 196 S.W.2d 913, 915 (Ark. 1946) (when a defendant's negligence "aggravates, or brings into activity, a dormant or diseases condition or one to which the injured person is predisposed, the defendant is liable to the injured person, for the full amount of the damages which ensue, notwithstanding such disease or weakened condition.").

[73] *Lapleine v. Morgan's L. & T.R. & S.S. Co.*, 4 So. 875 (La. 1888)

[74] *Id.* at 877.

of product users is held to be not defective or unreasonably dangerous.[75] This "idiosyncratic response" defense applies when the product would not be expected to cause similar health effects in a "normal" or "average" person.[76] The formalistic justification for this defense is that the hyper-susceptibility of the plaintiff, rather than the product, is the proximate cause of the plaintiff's injury.[77] The defense has been applied most frequently to allergic reactions to cosmetic products, but has also been applied in cases involving idiosyncratic responses to drugs and chemicals.[78] An adverse effect that is limited to people carrying a rare genetic susceptibility would thus also appear to fall within the scope of the idiosyncratic response defense.[79]

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[75]*E.g.,* Guilbeau v. W.W. Henry Co., 85 F.3d 1149, 1168-69 (5th Cir. 1996); Merrill v. Beaute Vues Corp., 235 F.2d 893, 897-98(10th Cir. 1956); Bennett v. Pilot Products Co., 235 P.2d 525, 526-27 (Utah 1951); Adelman-Tremblay v. Jewel Cos., 859 F.2d 517, 522-23 (7th Cir. 1988). *See* James A. Henderson, *Process Norms in Products Litigation: Liability for Allergic Reactions*, 51 U. PITT. L. REV. 761, 777-82 (1990); John Gerald Gleeson, *Idiosyncrasy: A Developing Defense in Drug and Hazardous Substances Litigation*, FOR THE DEFENSE, Apr. 1989, at 9.

[76]*Adelman-Tremblay*, 859 F.2d at 524; Presbrey v. Gillette Co., 435 N.E. 2d 513, 520 (Ill. App. 1982).; Joseph J. Ortego, Samuel Goldblatt & Kevin McElroy, *Idiosyncratic Reactions: A Limitation on the Duty to Warn*, MEALEY'S LITIG. REP'T: TOXIC TORTS, Oct. 20, 1999, at 29.

[77]*Adelman-Tremblay*, 859 F.2d at 522 ; Presbrey v. Gillette Co., 435 N.E. 2d at 520.

[78]*See* Alan E. Korpela, *Products Liability: Strict Liability in Tort Where Injury Results from Allergenic (Side-Effect) Reaction to Product*, 53 A.L.R.3d 298; W.R. Habeeb, *Seller's or Manufacturer's Liability for Injuries as Affected by Buyer's or User's Allergy or Unusual Susceptibility to Injury from Article*, 26 A.L.R.2d 963. The defense has also been applied in the occupational context. *See, e.g.*, Smith v. Service Tire Truck Center, Inc., 2000 WL 145817, *4, No. 98A-03-013-WCC (Del. Super. Jan. 19, 2000) (an employee's allergic reaction to workplace chemicals "resulted from his own peculiar predisposition rather than from the peculiar nature of his employment.").

[79]An idiosyncratic response as defined in the case law would likely include, and often result from, genetic susceptibilities. *See, e.g.,* Guilbeau v. W.W. Henry Co., 85 F.3d 1149, 1170 n.49 (5th Cir. 1996) (citing Webster's Dictionary, defining "idiosyncratic" as "peculiar to the individual"); Gleason, *supra* note 75, at 10 ("Chemical idiosyncrasy is a genetically determined abnormal reactivity to a chemical."). The defense would likely not apply to susceptibilities due to the more common genetic polymorphisms present in one percent or more of the population, as the most prevalent idiosyncracy to which the defense has been

The idiosyncratic response defense applies to both design defect and failure to warn claims under both negligence and strict liability standards.[80] Despite this broad application, the case law reveals two distinct theories of the defense, which affect its scope with respect to the duty to warn.[81] Some courts base the idiosyncratic response defense on the unforeseeability of the rare susceptibility in the exposed population.[82] These courts generally hold that a "normally safe" product that injures only a small number of susceptible individuals is not defective, but must be accompanied by a warning when the manufacturer knew or should have known of the potential for an idiosyncratic response, no matter how unusual.[83] Other courts apply a more instrumental rationale, emphasizing the undue burdens that liability would impose for

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applied to date afflicted 1 in 2000 people. *Bennett*, 235 P.2d at 526.

[80]*See Adelman-Tremblay*, 859 F.2d at 521-24 (no liability under either negligence or strict liability for idiosyncratic response); Presbrey v. Gillette Co., 435 N.E. 2d at 520 ("The rule barring the idiosyncratic consumer from recovery generally applies whether suit is brought under strict liability, breach of warranty, or tort.").

[81]Both theories provide a complete defense for design defect claims when the product injures only individuals with a sufficiently rare susceptibility, and thus the following discussion focuses only on failure to warn claims.

[82]*E.g.*, Merrill v. Beaute Vues Corp., 235 F.2d at 897 ("The essence of these decisions is that a reasonable person could not foresee the purchaser's condition and could not anticipate the harmful consequences."); Griggs v. Combe, Inc., 456 So.2d 790, 792 (Ala. 1984) ("If [defendant] could have no foreknowledge of this type of injury, it was not negligent in marketing the product, nor did it have a duty to warn of such an unreasonable risk.").

[83] Holladay v. Chicago, Burlington & Quincy Rd. Co., 255 F. Supp. 879, 884 (S.D. Ia. 1966); McEwan v. Ortho Pharmaceutical Corp., 528 P.2d 522, 530 (Or. 1974); Tomer v. American Home Products Corp., 368 A.2d 35, 40 (Conn. 1976); Basko v. Sterling Drug, Invc. 416 F.2d 417, 430 (2d Cir. 1969); Wright v. Carter Products, 244 F.2d 53, 58 (2d Cir. 1957).

a product that is safe for most people.[84] As one court put it, "[a] manufacturer has no duty to withhold its product from the market merely because the product may pose a risk to certain hypersensitive individuals."[85] These courts have usually held that the idiosyncratic defense applies, and thus there is no defect or duty to warn, even when the defendant knows or should know that there are likely to be a small number of unidentifiable susceptible individuals in the population.[86] The rationale for this approach is that the costs of warning outweigh the benefits, especially given that the warning is likely to be ineffective when the susceptible individuals are not aware of their sensitivity and thus would be unlikely to heed any warnings.[87]

Although the thin skull doctrine and the idiosyncratic response defense appear inapposite, courts generally apply one or the other of these doctrines without even mentioning the other. How can these

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[84] *E.g.*, Presbrey v. Gillette Co., 435 N.E. 2d at 520 ("The benefit to the mass public who use the product is said to outweigh the harm suffered by the insignificant few.").

[85] Bingham v. Terminix Intl. Co., 896 F. Supp. 642, 645 (S.D.Miss. 1995). Of course, this statement does not address the potential alternative that the product might be altered to make it less dangerous.

[86] *E.g.*, Kaempfe v. Lehn & Fink, 249 N.Y.S.2d at 845-46 ("in the case of a useful and reasonably safe product, in general use, the supplier owes no special duty of warning to the unknown few who constitute a mere microscopic fraction of potential users who may suffer some allergic reaction not common to the ordinary or normal person."); Adelman-Tremblay v. Jewel Cos., 859 F.2d at 517 (duty to warn of idiosyncratic response only when it occurs in an "identifiable class of sensitive users"); Merrill v. Beaute Vues Corp., 235 F.2d at 897; Blalock v. Westwood Pharmaceuticals, Inc., 1990 WL 10557 *2 (E.D. La. 1990); Tayar v. Roux Labs., Inc., 460 F.2d 494, 496 (10th Cir. 1972).

[87] As genetic testing becomes more widespread, however, it is likely that more consumers will be tested and have information about their potential genetic susceptibilities. If and when this occurs, the class of susceptible individuals may indeed become "identifiable," and the defense may no longer apply, at least with respect to the duty to warn. *See Adelman-Tremblay*, 859 F.2d at 517 (duty to warn of idiosyncratic response only when it occurs in an "identifiable class of sensitive users")

doctrines be reconciled? Which doctrine should apply to idiosyncratic genetic susceptibilities?[88] The application of the two doctrines appears to be largely a question of subject matter. The thin skull doctrine is applied typically in negligence cases to physical trauma from automobile and other accidents,[89] whereas the idiosyncratic response defense is applied most often to toxic injuries from pharmaceuticals, cosmetics, and other consumer products.[90]

In a physical trauma accident case, the initial inquiry is whether the defendant is at fault for the accident. In this first step of the analysis, the standard of care is based on whether the defendant's actions would offend the sensibilities of the "reasonable" or "normal" person in the community.[91] If, and only if, such responsibility is established, then a second independent inquiry is made into the plaintiff's injuries to determine what damages were caused by the defendant's tortuous act. Here, the plaintiff's unique sensitivity becomes relevant, and the thin skull doctrine holds the defendant, who has already been found to be culpable, liable for all damages to the plaintiff, even if they were unforeseeable and beyond those expected for a "normal" person. Thus, a plaintiff's unique susceptibilities are considered in the second step governing

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[88]*See* Margaret A. Berger, *Eliminating General Causation: Notes Towards a New Theory of Justice and Toxic Torts*, 97 COLUM. L. REV. 2117, 2128 n.48 (1997) ("should a defendant as a matter of policy be liable to subgroups within a population that have a genetic susceptibility that makes their relative risk considerably higher than two-fold, or is this a risk that members of a technological society must bear?").

[89]*See* Bahr & Graham, *supra* note 71, at 409 ("the thin skull principle is uniformly restricted to cases of personal injuries in negligent torts").

[90]*See supra* note 78.

[91]*See* Bahr & Graham, *supra* note 71, at 426-427 ("A sensitive person suffering harm will not suffice, as the harm must be judged against the suffering of a normal person in the community.").

damages, but not in the first step determining culpability.[92]

In contrast, for chemical, pharmaceutical or other products alleged to cause toxic injury, the fault or defect inquiry often collapses into the damages inquiry, because it is the existence and extent of injury caused by the product or activity that typically determines whether or not the product is defective.[93] If there is no harm, the defendant's actions in producing the product would not be negligent or faulty (and indeed would be favored), unlike in a trauma accident case where a defendant could still be negligent even though no damages resulted.[94] Thus, to the extent that culpability (as opposed to damages) is determined based on the sensitivities of a "normal" person, a defendant whose product only causes harm due to an unusual idiosyncratic response should not then be held responsible. Moreover, since some hypersensitivity reaction

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[92]*See* Soap Corp. of America v. Balis, 223 S.W.2d 957, 962 (Tex. 1949) ("The effect of the odors on persons of ordinary sensibilities was material in determining whether or not there was a nuisance. The maintenance of the nuisance was a tort. A right of damages for injuries proximately resulting from the nuisance was not limited to persons of ordinary sensibilities."), *cited in* Bahr & Graham, *supra* note 71, at 427; Glanville Williams, *The Risk Principle*, 77 L.Q. REV. 195 (1961) ("For the purpose of avoiding negligent conduct, the reasonable man has to consider the effect of his conduct upon ordinary people, but he is allowed to leave out of account, generally, the possibility of meeting exceptionally sensitive persons. The reason is that to require him to guard against such exceptional sensitivity would impose too great a restraint upon conduct. On the other hand, when it once held that the defendant has been negligent towards the plaintiff, because he should have foreseen injury to an ordinary person, the thin skull rule makes him liable for the full injury resulting from the special sensitivity. Thus, the thin skull rule ... perpetuates the distinction between the question of initial negligence and the question of extent of liability.").

[93]This analysis applies to products that may cause harm in the context of their intended, beneficial use. It may not apply to exposures that result from unintended releases of a chemical or other toxic agents into the environment as a result of the defendant's fault, such as spills, leaks or accidents - where fault is separable from the resulting injuries.

[94]Some scholars argue that such "negligence in the air," where the defendant has breached a duty of care but no injury results, does not establish a complete tort. *See* Ernest J. Weinrib, *Causation and Wrongdoing*, 63 CHI.-KENT. L. REV. 407, 430 (1987) (tort system treats causation and injury as a single unit). Notwithstanding this theoretical point, juries occasionally find that a defendant was negligent but award no damages because the plaintiff has incurred no compensable injuries.

to any chemical substance is inevitable within the general population, the question is necessarily one of acceptable or reasonable risk.[95] These factors compel a greater role for foreseeability in toxic injury cases compared to physical trauma cases,[96] and likewise argue against liability for a manufacturer whose beneficial product is "safe" for the general population and only injures genetically susceptible individuals.[97] Thus, the idiosyncratic response defense rather than the thin skull doctrine appears to be the appropriate standard for genetically susceptible plaintiffs, although the defense should be limited to require a warning when the genetic susceptibility can be identified in an individual.[98]

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[95]*See* Helene Curtis Industries, Inc. v. Pruitt, 358 F.2d 841, 858 (5th Cir. 1968) ("products which involve chemical reactions never have any tests which can guarantee absolute safety to all the consuming product"); Bennett v. Pilot Products Co., 235 P.2d at 527. ("Every substance, including food which is daily consumed by the public, occasionally becomes anathema to him particularly allergic to it..."); John D. Graham, *Historical Perspective on Risk Assessment in the Federal Government*, 102 TOXICOLOGY 29, 31 (1995) ("Toxicity, the capacity of a substance to produce serious bodily injury or death, is an inherent property of every chemical substance.").

[96]*See* Restatement (Third) Torts, § 2, Reporter's Note, comment m, at 102 ("There is no good reason to burden plaintiffs with proving the foreseeability of risks arising from foreseeable uses of mechanical products. Almost by definition, once the use if foreseeable, the risks that attend such use are foreseeable. Imputation of knowledge is limited to cases dealing with durable goods and specifically excludes prescription drugs, chemicals, and toxics from imputed knowledge.").

[97]One scholar justifies the "thin skull" doctrine on efficiency grounds, arguing that there will be few cases where a plaintiff's sensitivity matters, as most tortuous forces will injure both normal and brittle persons (e.g., airplane crash), and moreover any person so brittle that they would be injured by a force harmless to normal persons would likely have incurred such injury previously in the "hurley-burley world." A simple rule that asks only whether the force was sufficient to cause injury, without considering the sensitivity of the injured plaintiff will therefore usually produced the correct result . Richard A. Epstein, *Causation–In Context: An Afterward*, 63 U. CHI.-KENT L. REV. 653, 673-74(1987). This argument is less persuasive with respect to toxic risks, where widespread variations in susceptibility exist within the population, and which may play a role in a substantial percentage of toxic injuries.

[98]*See supra* note ?.

3. *Recovery for Latent Risk*

In recent years, toxic injury plaintiffs have frequently asserted, and have sometimes succeeded on, claims for recovery for latent risks that have not yet manifested into symptomatic disease. These claims include recovery for increased risk of future disease,[99] fear of developing future disease,[100] and medical monitoring costs.[101] These claims are all premised on the belief that the plaintiff has likely incurred genetic or other subcellular injury as a result of toxic exposures and is at an increased risk of future disease as a result of the progression of those present injuries.[102] Although traditional tort doctrine only provides recovery for manifest injury,[103] several arguments have been advanced for allowing recovery for latent risks. First, because of the long latency period of many toxic injuries, delaying litigation until disease manifests presents numerous practical problems including lost evidence, faded memories, and insolvent or otherwise

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[99] *E.g.*, Jackson v. Johns-Manville Sales Corp., 781 F.2d 394, 410-13 (5th Cir.), cert. denied, 478 U.S. 1022 (1986). *See generally* Donald F. Pierce, *Recovery for Increased Risk of Developing a Future Injury From Exposure to a Toxic Substance*, 19 ENVTL. L. REPTR. 10256 (1989).

[100] *E.g.*, Potter v. Firestone Tire & Rubber Co. 863 P.2d 795 (Cal. 1993). *See generally* Bill Charles Wells, *The Grin Without the Cat: Claims for Damages from Toxic Exposure Without Present Injury*, 18 WM. & MARY J. ENVTL. L. 285, 309-19 (1994).

[101] *E.g.*, Ayers v. Township of Jackson, 525 A.2d 287, 291-92 (N.J. 1987). *See generally* James M. Garner, Keith A. Kornman & Jon B. Coats, *Medical Monitoring: The Evolution of a Cause of Action*, 30 ENVTL. L. REPTR. 10024 (2000)

[102] While courts apply somewhat different standards for evaluating increased risk, fear of disease, and medical monitoring costs claims, these risk-based claims are addressed collectively here because they are all based on the existence of latent risk, which biomarkers may help to identify and quantify.

[103] *See* PROSSER AND KEETON ON TORTS (5th ed. 1984) §30, at 165 ("the threat of future harm, not yet realized, is not enough.").

judgment-proof defendants.[104] Second, allowing claims for latent risks will avoid many of the statute of limitations and claim-splitting problems that plaintiffs may encounter when the effects of toxic exposure are spread over time.[105] Third, allowing plaintiffs to recover for latent risks may better deter risk-creation.[106]

Notwithstanding the force of these arguments, many courts have expressed strong reservations about the practical impact of recognizing risk-based claims. Proof of latent risk has (to date) tended to be highly speculative,[107] and allowing such claims may open a floodgate of additional legal claims.[108] Moreover, allowing recovery for latent risk would likely result in "windfalls for those who never take ill and insufficient compensation for those who do."[109] Finally, if a plaintiff *may* recover for latent risk, then a plaintiff perhaps *must* seek such recovery when the increased risk is discovered or risk having the statute of limitations run.[110]

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[104]Christopher H. Schroeder, *Corrective Justice and Liability for Increasing Risks*, 37 UCLA L. REV. 439, 475-76 (1990); Note, Tort Actions for Cancer: Deterrence, Compensation and Environmental Carcinogenesis, 90 YALE L.J. 840, 851 (1981).

[105]*See Developments in the Law: Toxic Waste Litigation*, 99 HARV. L. REV. 1458, 1604-09 (1986); Note, *Increased Risk from Hazardous Waste: A Proposal for Judicial Relief*, 60 WASH. L. REV. 635, 644 (1985).

[106]Schroeder, *supra* note 104, at 473; Glen O. Robinson, *Probabilistic Causation and Compensation for Tortuous Risk*, 14 J. LEGAL STUD. 779, 784 (1985); W.L.F. Felstiner & Peter Siegelman, *Neoclassical Difficulties: Tort Deterrence for Latent Injuries*, 11 LAW & POL'Y 309 (1989).

[107] Schweitzer v. Consolidated Rail Corp, 758 F.2d 936 (3d Cir.), *cert. denied*, 474 U.S. 864 (1985); Anderson v. W.R. Grace & Co., 628 F. Supp. 1219, 1232 (D.Mass. 1986)

[108]Metro-North Commuter Rd. Co., v. Buckley, 521 U.S. 424, 433 (1997); Potter v. Firestone Tire & Rubber Co., 863 P.2d 795, 809-810 (Cal. 1993); Ayers, 525 A.2d at 307.

[109]Schweitzer, 758 F.2d at 942.

[110]Burns v. Jaquays Mining Corp., 752 P.2d 28, 31 (Az. Ct. App. 1987).

The courts have accordingly limited recovery for latent risks by establishing, in the words of the U.S. Supreme Court, "recovery-permitting categories the contours of which more distantly reflect [these] abstract general policy concerns."[111] For example, most courts have limited recovery for increased risk and fear of future disease to plaintiffs who can demonstrate a present injury,[112] and many have also required plaintiffs to demonstrate a sufficiently large quantum of increased risk.[113] These recovery-limiting categories are intended to ensure that latent risks for which plaintiffs seek recovery are both substantial and objectively ascertainable.[114] At the same time, these requirements impose a high threshold to recovery that most plaintiffs cannot surmount.

Biomarkers of disease precursors may help plaintiffs meet the legal hurdles set by courts to limit recovery for latent risk, as well as to enhance the factual and policy imperatives for such recovery.[115] In the case law to date, several courts have allowed expert testimony that the plaintiff likely incurred genetic

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[111]Metro-North Commuter Rd. Co. v. Buckley, 521 U.S. 424, 436 (1997). *See also* Wells, *supra* note 100, at 314-19.

[112]*E.g.*, Adams v. Johns-Manville Sales Corp., 783 F.2d 589, 591-93 (5th Cir. 1986); Ayers v. Township of Jackson, 525 A.2d at 287; Burns v. Jaquays Mining Corp., 752 P.2d at 31-32; Anderson v. W.R. Grace & Co., 628 F. Supp. 1219, 1226-27 (D.Mass. 1986).

[113]Sterling v. Velsicol, 855 F.2d at 1205 (requiring greater than 50 percent chance of developing disease to recover for increased risk); *Potter*, 863 P.2d at 807-816 (requiring showing that disease is more likely than not to recover for fear of future disease); In re Paoli Rd. Yard PCB Litigation, 916 F.2d 829, 852 (3d Cir. 1990) (requiring showing of "significantly increased risk" for medical monitoring damages).

[114]One commentator has referred to the present injury requirement as a "hurdle" to screen out speculative claims, and the requirement for the future risk to be sufficiently large as a "floor," which screens out inconsequential claims. Wells, *supra* note 100, at 314-315.

[115]*See* ASHFORD *et al.*, *supra* note 6, at 158; Kanner, *supra* note 6, at 350 ("Modern medical science enables us to see 'risk' as present chromosomal damage or immunological damage.").

or other subcellular injury from a toxic exposure to establish the "present injury" on which a latent risk claim can be anchored.[116] In most of these cases, the existence of the genetic injury was hypothesized rather than shown with objective evidence.[117] Given this lack of empirical proof, other courts have required "objective symptomatology" to establish a present physical injury, holding insufficient unverified allegations of genetic or subcellular damage.[118] Presumably even these courts would be more inclined to accept latent risk claims if based on objective and validated biomarkers of effect.[119] Such biomarkers would not only help to alleviate concerns about speculative or fraudulent claims, but would also validate the plaintiff's anxiety and medical need for ongoing monitoring.[120] Conversely, the absence of any such biomarkers of effect,

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[116]*E.g.,* Brafford v. Susquehanna Corp., 586 F. Supp. 14 (D.Colo. 1984) (expert allegation of chromosomal aberrations from radon exposure sufficient to establish triable issue of present injury); Askey v. Occidental Chemical Corp., 477 N.Y.S.2d 242, 247 (N.Y. App. Div. 1984)("persons exposed to toxic chemicals emanating from the landfill have an increased risk of invisible genetic damage and a present cause of action for their injury"); Anderson v. W.R. Grace & Co., 628 F. Supp. at 1226-27 (subcellular injury substantiated by expert testimony meets requirement of "objective symptomatology"); Werlein v. United States, 746 F. Supp. 887, 901 (D. Minn.1990) (expert testimony of likelihood of chromosome breakage sufficient to establish present injury).

[117]*But see* Caputo v. Boston Edison Co., 1990 WL 98694 (D. Mass., July 9, 1990),*aff'd*, 924 F.2d 11 (2d Cir. 1991) (plaintiff's claim of physical injury at the "chromosomal cellular level" rejected after cytogenetic testing demonstrated that the frequency of chromosomal alterations in the plaintiff was within normal levels).

[118]*E.g.,* Payton v. Abbott Labs, 437 N.E.2d 171, 181 (Mass. 1982); Schwietzer v. Consolidated Rail Corp., 758 F.2d at 942; Jackson v. Johns-Manville Sales Corp. 781 F.2d at 412 n. 22.

[119]*See* Kanner, *supra* note 6, at 356.

[120]*Id.* at 350. *Cf.* Merry v. Westinghouse Electric Co., 684 F. Supp. 847, 851 (M.D.Pa. 1988) ("Human populations show even wider variability in response to toxic agents in large part because of their heterogeneous genetic make up. Currently, it is difficult to predict which individuals are likely to be most sensitive and therefore at highest risk. Therefore, it is prudent to monitor everyone whom is exposed as if they constitute the highest risk.").

especially when such biomarkers would normally be expected, may allay the plaintiffs' fear of future cancer, as well as bar recovery for latent risk.[121]

The power of biomarkers to validate latent risk claims is demonstrated by the following hypothetical. A young woman is exposed to vinyl chloride emitted by a nearby factory. A blood test reveals the presence of DNA adducts in her lymphocytes that are consistent with a significant recent exposure to vinyl chloride. Two years later, the women gets pregnant and has a son, who genetic testing reveals has a mutation that inactivates ("knocks out") one of his two copies of the *p53* tumor suppressor gene. The mutation has the "genetic fingerprint" that is characteristic of vinyl chloride.[122] Genetic testing of the mother reveals that most of her cells contain no such mutation, although a few of her cells have similar mutations. Moreover, other sequence variations in the mother's *p53* genes confirm that the son's defective copy of the gene came from the mother, thus indicating that the mutation must have arisen in the mother's germ cells. With only one functioning copy of the *p53* gene, the son is at a permanent significantly increased risk of cancer, although he presently experiences no symptoms or disease. A mutation to the remaining functional copy of the *p53* gene, arising either spontaneously or from some other exposure later in life, would almost certainly result in cancer.[123] By providing objective and specific evidence of an increased risk and the

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[121]*See* Laxton v. Orkin Exterminating Co., Inc., 639 S.W.2d 431, 434 (Tenn. 1982) (reasonable basis for fear of future disease, and cause of action for such fear, evaporated when negative blood tests indicated that plaintiff would suffer no further harm).

[122]*See supra* note 38.

[123]*See* Semenza & Weasel, *supra* note 38, at 155 (inactivation of *p53* can occur from exposure to environmental mutagens or sporadically due to endogenous processes). Moreover, research indicates that the loss of one copy of a tumor suppressor gene such as *p53* gene greatly increases the likelihood of spontaneous loss of the second copy of the gene, which is called "loss of heterogeneity." *See* ROBERT A. WEINBERG, ONE RENEGADE CELL 75-76 (1998).

probable cause of such risk, the genetic biomarker in this example significantly strengthens the case for such a plaintiff to recover damages for his permanent and irreversible risk.

More generally, it is now known that most or all cancer results from a series of several sequential genetic mutations, which now can potentially be identified.[124] As such mutations are detected in exposed individuals, courts will face the issue of how to allocate liability among several sequential causes of an incipient tumor, each of which was a necessary but not sufficient cause of the cancer. In addition, the tort system will need to decide whether plaintiffs who can demonstrate that they have sustained mutations in this chain of causation, but who have not yet developed cancer, can seek damages for their permanent and irreversible increased risk of cancer. An additional complication is that variations in genetic susceptibility between individuals could dramatically affect the increased risk from a particular exposure or mutation.[125] Thus, while resolving the need for objective proof of latent risk in many cases, biomarkers are likely to create a new set of difficult questions for courts to address.

4. Plaintiffs Assumed Risk

A defendant could argue that a plaintiff who was aware of her genetic susceptibility to a product or activity, but nevertheless subjected herself to that product or activity, thereby assumed the risk of any adverse consequences that followed.[126] Such a defense requires the defendant to demonstrate that

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[124]*See* Hattis & Swedis, *supra* note 18, at __[this volume]; WEINBERG, *supra* note 123, at 45-53.

[125]In Elam v. Alcolac, Inc., 765 S.W.2d 42 (Mo. App. 1988), the plaintiffs' expert testified that he could not quantify the plaintiffs' increased risk of cancer because "each person, based on their genetic constitution, is at different risks." *Id.* at 208.

[126]This defense could be styled as "assumption of risk" or "contributory negligence," depending on the jurisdiction, although in some jurisdictions the two defenses have merged. *See* Restatement(2d) of Torts, §402A, comment N; PROSSER & KEETON, *supra* note 103, at 448.

the plaintiff had knowledge of the potential risk, but nevertheless undertook that risk voluntarily.[127] The defense may apply not only when a plaintiff knew she was genetically susceptible to a particular product or exposure, but also when the plaintiff who was unaware of her susceptibility was warned to obtain a genetic test of possible susceptibility and failed to get tested. An analogy is provided by cases in which a court has found assumption of risk or contributory negligence when the plaintiff failed to take a "patch test" prior to use of a cosmetic product as recommended by the manufacturer to test for allergic reactions.[128]

An employer might rely on a similar defense with respect to genetically susceptible workers in its workplace. One option would be to offer genetic susceptibility testing to workers, provide them with an appropriate warning of the risks to susceptible workers, and then give each worker the choice of whether to continue in their present position. Another option would be to inform workers of the genetic susceptibility in the population, and to recommend that the workers seek genetic testing. Assertion of the assumption of risk defense might be a closer question in this second context because none of the workers would know that they were specifically at a higher risk as a result of the employer's warning (unless they took the initiative to get genetically tested). Moreover, the assumption of risk doctrine is limited in the occupational context to the extent that the employee is often forced to continue working (and thus continue to incur the associated risk) by economic necessity.[129] The assumption of risk defense in the employment context may thus depend

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[127]*See, e.g.*, Shufelberger v. Worden, 369 P.2d 382, 383 (1962); Green v. APC, 960 P.2d 912, 918 (1998).

[128]*E.g.*, Thomas v. Gillette Co., 230 So.2d 870, 876 (La.App.), cert. denied, 233 So.2d 249 (1970); Quiroz v. Max Factor, Inc., 264 So.2d 263, 266 (Ct.App. La. 1972); Arata v. Tonegato, 314 P.2d 130, 133 (Ct.App. Cal. 1957).

[129]*See, e.g.,* Prentiss v. Kirtz, 374 N.E. 429, 431 (Ct. App. Ohio 1977); Santiago v. Becton Dickinson & Co., 571 F. Supp. 904, 915 (D. P.R. 1983).

on the employee's options for less hazardous work, such as the offer by the employer of less hazardous job functions with comparable employment benefits or the availability of protective equipment or other preventive measures in the current workplace.[130]

B. Causation

1. Plaintiff At Higher Relative Risk than General Population

One of the most formidable obstacles that injured plaintiffs face in toxic injury litigation is to demonstrate that the defendant's product or action was more likely than not to have caused the plaintiff's injuries.[131] Courts often favor epidemiological data to establish such causation.[132] In addition, many courts have required plaintiffs to demonstrate that they face a relative risk of at least two, which represents a doubling of risk over the background risk in the general population, in order to satisfy the preponderance of evidence standard.[133] Relative risks greater than two are relatively rare with respect to the types of

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[130]Brady v. Ralph M. Pasons Co., 609 A.2d 297, 304 (Ct. App. Md 1992) (economic compulsion exception to assumption of risk does not apply when employee not compelled or threatened with loss of employment to undertake hazardous activity).

[131]*See, e.g.,* David Rosenberg, *The Causal Connection in Mass Exposure Cases: A "Public Law" Vision of the Tort System*, 97 HARV. L. REV. 849, 855-56 (1984); In re "Agent Orange" Product Liability Litigation, 597 F. Supp. 740, 833-35 (E.D.N.Y. 1984).

[132]*E.g.*, Brock v. Merrell Dow Pharmaceuticals, Inc., 874 F.2d 307, 312 (5th Cir. 1989) (lack of epidemiological proof "fatal" to plaintiff's case); In re Breast Implant Litigation, 11 F. Supp.2d 1217, 1224 (D. Col. 1998) ("Epidemiology is the best evidence of causation in the mass torts context."). *But see* Christophersen v. Allied-Signal Corp., 902 F.2d 362, 367 (5th Cir. 1990) (epidemiology evidence not always needed to prove causation).

[133]*E.g.*, Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1321 (9th Cir. 1995); In re "Agent Orange" Product Liability Litigation, 597 F. Supp. at 833-34; Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387, 1403-4 (D. Or. 1996). *But see* In re Joint E. & S. Dist. Asbestos Litig., 52 F.3d 1124,1134 (2d Cir. 1995) (it is a question for the jury "whether many studies over the 1.0 mark have any significance in combination"); Sander Greenland & James M. Robins, *Epidemiology, Justice, and the*

exposures usually involved in toxic injury litigation.[134]

A plaintiff might be able to overcome the problem of demonstrating a doubling of risk if she can demonstrate that she is at a greater increased risk from exposure to the toxic agent relative to the general population because of a genetic susceptibility.[135] Most epidemiology studies to date do not differentiate by genetic background, and thus the aggregate data in such studies provide an "average" risk estimate for the overall population that does not provide an accurate measure for the different genetic subgroups within that population.[136] For example, an aggregate population risk estimate that appears to indicate no association between exposure and injury may mask a strong association in a particular genetic subgroup within that population. Thus, if epidemiological data suggest that exposure to a particular product increases the risk of a particular type of cancer by 20 percent over the background rate (i.e., relative risk =1.2), the plaintiff

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Probability of Causation, 40 JURIMETRICS 1 (2000) (criticizing requirement for relative risk greater than two).

[134]*See* Perera, *supra* note 16, at 1072 ("In epidemiology, it has been difficult to detect relative risks of 1.5 or even 2.0."); Gary Taubes, *Epidemiology Faces Its Limits*, 269 Science 164, 165 (1995) (only a handful of carcinogenic agents have produced relative risk greater than two in epidemiology studies). An exception is "signature diseases" that are exclusively or at least predominantly associated with exposure to a particular toxic substance, such as mesothelioma due to asbestos exposure or hepatic angiosarcomas associated with vinyl chloride. *See* Daniel A. Farber, *Toxic Causation*, 71 MINN. L. REV. 1219, 1251-52 (1987); Berger, *supra* note 88, at 2121 n.16.

[135]*See* Poulter, *supra* note 48, at __ (this volume) for a discussion of statistical complications and evidentiary limitations raised by this use of genetic susceptibilities.

[136]*See* O. Shpilberg, *et al.*, *The Next Stage: Molecular Epidemiology*, 50 J. CLIN. EPIDEMIOLOGY 633, 637 (1997) ("A 1.5-fold relative risk may be composed of a 5-fold risk in 10% of the population, and 1.1-fold risk in the remaining 90%, or a 2-fold risk in 25% and a 1.1-fold for 75%, or a 1.5-fold risk for the entire population."); Louis Anthony Cox, Jr., *Statistical Issues in the Estimation of Assigned Shares for Carcinogenesis Liability*, 7 RISK ANALYSIS 71, 76 (1987); Berger, *supra* note 88, at 2128.

could argue that this figure is only a population average, and that she, because of her genetic susceptibility, is at a significantly higher risk.[137]

Residents living near the Hanford Nuclear Reservation in Washington State recently attempted to use the existence of genetically susceptible subgroups to meet their burden of proof that radioactive emissions from the facility caused their thyroid cancer.[138] The court required as a precondition for submitting their claims to the jury that the plaintiffs establish that they had received a dose sufficient to double their risk of thyroid cancer.[139] In calculating such "doubling doses," the plaintiffs' expert adjusted his estimate by a factor of five to account for genetic susceptibility within the population.[140] The court rejected this adjustment as both unreliable and irrelevant because "of the present reality that there is no way to identify persons who are allegedly more susceptible to radiation-induced thyroid cancer, nor can alleged

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[137]As one court noted, "relative risk is a term that applies to a population, not to an individual. While it is possible to estimate the average increased risk for members of a population, it is really not appropriate to assume that each individual in a population actually had a similar risk. It is much more appropriate to believe that the average increased risk is made up of a wide range in individual risks in the population...." Hall v. Baxter Healthcare Corp., 947 F. Supp. at 1450-51. *See also* Mark Parascandola, *What Is Wring With the Probability of Causation?*, 39 JURIMETRICS 29, 35 (1998) ("decisionmakers could focus on the relative risk for a subpopulation that bests fits the plaintiff, rather than the relative risk for the population at large"); Berger, *supra* note 88, at 2127 ("At this time, judges disagree about the admissibility of a study with a risk ratio of less than 2.0 when plaintiff can point to personal factors that might cause his or her risk to be higher.").

[138]In re Hanford Nuclear Reservation Litigation, 1998 WL 775340 (E.D. Wash. 1998).

[139]*Id.* at *8-11.

[140]*Id.* at *64. The expert explained that if "we assume the development of human cancer is like filling a glass, which when filled leads to a growing cancer, ... [t]he effect of the concept of genetic susceptibility to cancer ... is that the glass for such individuals is smaller, and thus more easily filled." *Id.*

differences in susceptibility be quantified."[141] As more biomarkers of genetic susceptibility are identified and validated, however, it may soon be feasible to identify susceptible individuals and to quantify their risk, as required by the court. That court also criticized plaintiffs' application of a genetic susceptibility factor to the entire population, noting that to the extent there are some individuals in the population that are more susceptible than average to radiation, there must necessarily be some people less sensitive than the population average.[142] Thus, evidence of relative genetic susceptibility may be two-edged sword -- it could benefit those plaintiffs that are more sensitive than average to a particular exposure, but disadvantage those plaintiffs who are more resilient.[143]

An argument that the plaintiffs have an increased susceptibility and therefore may have been harmed by the defendant's product even if the evidence does not show a doubling of risk for the "average" person has been employed by plaintiffs with some success in other cases.[144] For example, some silicone

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[141] *Id.* at *70.

[142] *Id.* at *66-68. The court cited approvingly from the defendant's brief the following argument: "If [plaintiffs' expert] wants to adjust these baseline risk estimates for persons of greater susceptibility, then he must first remove them from the underlying epidemiological studies, because their inclusion skews the risk estimates upwards due to their greater susceptibility. Once the hypersensitive are factored out of the underlying studies, the risk estimates for the remaining population should drop, and the doses necessary to prove generic causation should rise." *Id.* at 68.

[143] *See* M.T. Smith & L. Zhang, *Biomarkers of Leukemia Risk: Benzene as a Model*, 106 (Suppl. 4) ENVTL. HEALTH PERSPECT, 937, 940 (1998) (describing an inherited polymorphism in the *MPO* gene that when homozygous appears to lower the risk of benzene toxicity); Frederica P. Perera, *Uncovering New Clues to Cancer Risk*, SCI. AMERICAN, May 1996, at 54, 61 ("certain genetic traits may protect against one type of cancer, but may predispose to another").

[144] *E.g.,* Hand v. Norfolk Southern Ry., 1998 WL 281946, *6, No. 03A01-9704-CV-00123 (Tenn. Ct. App. 1998) (upholding judgment for plaintiff based in part on expert's testimony that plaintiff may have had individual susceptibility affecting the way he metabolized substances); Collins v. Hygenic Corp., 739 P.2d 1073 (Or. Ct. App. 1987) (exposure to chemical at levels two orders of magnitude below

breast implant plaintiffs argued that they were genetically susceptible to silicone in an attempt to overcome epidemiological studies showing no, or at most very small, increases in the relative risk of autoimmune disease in breast implant recipients.[145]

There is, however, a flaw in the argument that a genetically susceptible individual necessarily comes closer to satisfying the more likely than not standard than an "average" person. It is important to distinguish between genetic variants that increase susceptibility to a particular toxicological endpoint (*e.g.*, cancer) and those that increase sensitivity to a specific product.[146] If the former, many different factors might precipitate the disease in the predisposed plaintiff, and the probability that it was caused by defendant's product may decrease rather than increase because of the proliferation of potential alternative causes.[147] It is therefore incorrect to argue that because a plaintiff contains a genetic susceptibility, she

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"recognized safety levels" nevertheless found to be cause of illness in plaintiff with unusual susceptibility).

[145]*See, e.g.*,, V.L. Young, et al., *HLA Typing in Women with Breast Implants*, 96 PLASTIC & RECONSTRUCTIVE SURG. 1497 (1995); Ernest H. Hornsby & Dianna Pendleton, *Plaintiffs Mounting Case Against Silicone Gel Breast Implants*, 6 No. 4 MED/LEGAL ASPECTS OF BREAST IMPLANTS 4, at *5 (March 1998); Hall v. Baxter Healthcare Corp., 947 F. Supp. at 1456 (discussing and rejecting as too speculative plaintiffs' arguments about increased genetic susceptibility to silicone breast implants).

[146]*See* R. Julian Preston, *Interindividual Variations in Susceptibility and Sensitivity: Linking Risk Assessment and Risk Management*, 111 TOXICOLOGY 331, 332 (1996) (distinguishing genetic *susceptibility* to a disease from genetic *sensitivity* to an environmental stress); Harri Vainio, *Biomarkers in Metabolic Subtyping--Relevance for Environmental Cancer Control*, 20 ARCH. TOXICOL. SUPPL. 303, 304 (1998) (same).

[147]*See, e.g.*, National Bank of Commerce v. Associated Milk Producers, Inc., 22 F. SUPP..2d 942, 966 (E.D. Ark. 1998), *aff'd*, 191 F.3d 858 (8th Cir. 1999) (rejecting plaintiff's argument that his increased susceptibility to cancer as a result of his allergies necessarily increased the likelihood that aflaxtoxin from defendant's product was the cause of his laryngeal tumor, because if his "allergic condition makes him more susceptible to carcinogens, then he would be more susceptible to tobacco smoke, a carcinogen that is known to cause from 75% to 90% of all laryngeal cancer.").

necessarily has an increased relative risk from a particular exposure.[148] Rather, genetic susceptibility suggests that epidemiology studies on the general population may not be applicable in assessing causation, and epidemiological data focusing on a specific subgroup with the same genetic characteristic is needed to evaluate the effects of exposure on relative risk.

2. *Chemical-Specific Markers of Effect*

Even if a plaintiff establishes that a toxic exposure causes a doubling of background risk for a particular disease (general causation), the plaintiff usually must still prove that the exposure caused the disease in her (specific causation).[149] Substance-specific biomarkers of exposure may be able to provide the "particularistic" evidence necessary, and currently often unavailable,[150] to establish specific causation.[151] For example, some chemicals interact with the human body to produce a specific fingerprint or "signature"

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[148]The relevant inquiry for purposes of a causation determination is the risk to an exposed susceptible person relative to a non-exposed susceptible person, not the relative risk of a susceptible to a non-susceptible individual.

[149]*E.g.,* Raynor v. Merrell Pharmaceuticals, Inc., 104 F.3d 1371, 1376 (D.C. Cir. 1997). *See* Richard W. Wright, *Causation, Responsibility, Risk, Probability, Naked Statistics, and Proof: Pruning the Bramble Bush by Clarifying the Concepts*, 73 IOWA L. REV. 1001, 1054 (1988) ("particularistic" evidence necessary to establish individual causation).

[150]*See* Rosenberg, *supra* note 131, at 869 ("The short answer to the demand for 'particularistic' evidence of causation in mass exposure cases is that no such evidence can be produced."); In re "Agent Orange" Product Liability Litigation, 597 F. Supp. 740, 836 (E.D.N.Y. 1984) ("In mass exposure cases, ... the chance that there would be particularistic evidence is in most cases quite small....").

[151]*E.g.,* Elam v. Alcolac, 765 S.W.2d 42, 89-164 (Mo. App. 1988) (immunological and enzymatic biomarkers used to establish causation of "chronic systemic chemical intoxication" in plaintiffs exposed to toxic emissions); Sutera v. Perrier Group of America, Inc., 986 F. Supp. 655, 658-59, 664 (D. Mass. 1997) (plaintiff claimed that translocation between chromosomes 15 and 17 served as unique biomarker that demonstrated that benzene in Perrier caused his leukemia; court rejects argument after plaintiff's and defendant's experts agree that other chemicals can cause same translocation).

of effect, such as a chemical-specific DNA adduct or a particular spectrum of mutational change.[152]

Silicone breast implant plaintiffs relied prominently on studies claiming that various antibody and other biological markers of physiological response to silicone could be used to identify breast implant recipients with autoimmune disorders caused by their leaking implants.[153] By purporting to establish an objective biological relationship between silicone and an immunological response (represented by the presence of the biomarker), this biomarker evidence appeared to play a critical role in the decisions of several juries to award large damages to silicone breast implant plaintiffs.[154]

This reliance on biomarkers of effect in the silicone breast implant litigation was problematic, however. The biomarkers relied on were often not specific to silicone, and had little or no probative value on whether breast implants caused such disease, even though the evidence was often introduced for that purpose.[155] More generally, many if not all of the alleged biomarkers were scientifically suspect. For

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[152]*See supra notes* 30-? & 38 and accompanying text; Ellinger, *supra* note 6, at 44.

[153]*E.g.*, S.A. Tenenbaum, *et al.*, *Use of Antipolymer Antibody Assay in Recipients of Silicone Breast Implant Recipients*, 349 LANCET 449 (1997); D.L. Smalley, D.R. Shanklin, M.F. Hall, M.V. Stevens & A. Hannissian, *Immunologic Stimulation of T-lymphocytes by Silica After Use in Silicone Mammary Implants*, 9 FASEB J. 424 (1995). *See* Gary Taubes, *Silicone in the System*, DISCOVER, Dec. 1995, at 65.

[154]*E.g.,* Hopkins v. Dow Corning Corp., 33 F.3d 1116, 1125 (9th Cir. 1994) (upholding jury verdict for silicone breast implant recipient based in part on testimony of plaintiff's expert testimony on presence of silicone biomarkers); Baxter HealthCare Corp. v. Grimes, 1998 WL 5487729, No. 05-95-01682-CV (Tex.App., Aug. 31, 1998) (same); Vassallo v. Baxter Healthcare Corp., 696 N.E.2d 909, 917 (Mass. 1998) (same). *See* Taubes, *supra* note 153, at 66 (jurors who awarded $25 million verdict to breast implant recipient stated in subsequent interviews that the silicone immune biomarker testimony was "critical" to plaintiff's success).

[155] As one court observed in rejecting such evidence, the plaintiff's expert "has found that the Plaintiff possesses anomalous antibody levels in her blood chemistry; this anomaly leads him, based upon his observations with other women, to conclude that the Plaintiff's condition is implant-related. ... However,

example, a private physician, suspicious about one silicone sensitivity test that was relied on in many court cases,[156] sent to the laboratory that developed the test twelve blood samples from women who never had breast implants, but whose medical records were fabricated to indicate breast implantation. The testing laboratory reported back that eleven of the twelve women tested positive for silicone, raising serious doubts about the reliability of the diagnostic test.[157] Another silicone biomarker test used extensively in litigation could not be replicated by independent laboratories,[158] and was the subject of a warning letter from the Food and Drug Administration.[159] More generally, large, independent epidemiology studies failed to find any association between silicone breast implants and the various biomarkers relied on by plaintiff experts,[160]

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the witness admits that if the Plaintiff did not have breast implants but had the exact same symptoms and blood chemistry, then his diagnosis would have been non- implant-caused Sjogren's Syndrome.... Essentially, this is a bit like saying that if a person has a scratchy throat, runny nose, and a nasty cough, that person has a cold; if, on the other hand, that person has a scratchy throat, runny nose, nasty cough, and wears a watch, they have a watch-induced cold." Kelley v. American Heyer-Schulte Corp., 957 F. Supp. 873, 882 (W.D. Tex. 1997), aff'd, 139 F.3d 899 (5th Cir. 1998).

[156]*See, e.g.,* Allison v. McGhan Medical Corp., 184 F.3d 1300, 1317-19 (11th Cir. 1999); Toole v. McLintock, 778 F. Supp. 1543 (M.D. Ala., 1991), vacated in part, 999 F.2d 1430 (11th Cir. 1993); Vasallo v. Baxter Healthcare Corp., 696 N.E.2d 909, 912 (Mass. SJC 1998).

[157]V. Leroy Young, *Testing the Test: An Analysis of the Reliability of the Silicone Sensitivity test (SILS) in Detecting Immune-Mediated Responses to Silicone Breast Implants*, 97 PLASTIC & RECONSTRUCTIVE SURGERY 681 (1996).

[158]*See* Taubes, *supra* note 153, at 70 (Dr. Kossovsky's results could not be replicated by Scripps Research Institute scientists).

[159]FDA, Warning Letter (Regulatory Letter) 7/15/94 to Structured Biologicals (SBI) Laboratories: Detecsil Silicone Sensitivity Test (July 15, 1994) (copy on file with author); *see also* Taubes, *supra* note 153, at 74.

[160]*E.g.,* Sherine E. Gabriel, *et al.*, *Risk of Connective-Tissue Diseases and Other Disorders After Breast Implantation*, 330 NEW ENG. J. MED. 1697, 1699 (1994); Jorge Sanchez-Guerrero *et al.*, *Silicone Breast Implants and the Risk of Connective-Tissue Diseases and Symptoms*, 332 NEW ENG.

and several expert scientific reviews concluded that such silicone biomarkers were not valid or reliable.[161]

While the silicone biomarker evidence was quite successful in earlier breast implant trials, as the scientific doubts about the biomarker evidence accumulated, more and more courts refused to admit expert testimony based on such evidence.[162] This example demonstrates that biomarkers of effect, by purporting to provide an objective diagnostic link between exposure to a toxic substance and disease, can be helpful to plaintiffs in establishing causation. It also demonstrates that the reliability and medical significance of many biomarkers are likely to be controversial, and that litigants are prone to place premature or undue reliance on biomarkers that have not been properly validated.

The absence of biomarkers of effect can likewise be used by a defendant to argue against causation. This is demonstrated by a case in which the plaintiff was exposed to the pesticide aldecarb and complained of weakness, nausea, dizziness, blurred vision and abdominal cramps, which are all symptoms of aldecarb poisoning.[163] However, serum and blood tests failed to show any reduction in the plaintiff's cholinesterase levels, which the evidence before the court indicated was an objective and reliable biomarker

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J. MED. 1666, 1669 (1995).

[161]*E.g.,* INSTITUTE OF MEDICINE, SAFETY OF SILICONE BREAST IMPLANTS 198-214 (2000); Submission of Rule 706 National Science Panel Report, Chapter II. Clinical Immunology, In re: Silicone Breast Implant Products Liability Litigation (MDL 926) (N.D. Ala. Nov. 30, 1998); Independent Review Group, Silicone Gel Breast Implants (Jul 1998) (available at http://www-silicone-review.gov.uk) (scientific panel established by UK Chief Medical Officer). *See also* Pick v. American Medical Systems, Inc., 958 F. Supp. 1151, 1165-66 (E.D.La. 1997) (citing statements critical of silicone antibody testing by the Food and Drug Administration, Center for Disease Control, and College of American Pathologists).

[162]*E.g.*, Kelley v. American Heyer-Schulte Corp., 957 F. Supp. at 882-883; Allison v. McGan, 184 F.3d at 1317-19; Minnesota Mining & Atterbury, 978 S.W.2d 183, 200 (Tx. Ct. App. 1998); Hall v.Baxter Healthcare Corp., 947 F. Supp. at 1409-10, 1456-59.

[163]Polk Nursery Co., Inc. v. Riley, 433 So.2d 1233, 1234 (Fla. Dist. Ct. App. 1983).

of aldecarb exposure.[164] Relying on this biomarker evidence, the appeals court over-turned the award of workers' compensation benefits to the plaintiff, and attributed the plaintiff's symptoms to a "psychological reaction to a perceived but non-existent poisoning."[165] This case again confirms the heavy reliance that legal fact finders are likely to give the "objective" evidence provided by biomarkers.

3. Dosimetric Measure of Exposure to Toxic Agent

Courts generally require plaintiffs to demonstrate, and often quantify, exposure to defendant's product with objective data.[166] Yet, available evidence of exposure is often indirect, circumstantial or even non-existent.[167] Biomarkers can provide objective qualitative or quantitative proof of exposure. For example, plaintiffs have successfully relied on detection and measurement of a toxic substance in their blood to demonstrate exposure.[168]

Cytogenetic biomarkers of radiation exposure figured prominently in the Three Mile Island ("TMI") litigation, where the "critical issue" was the inability of nearby residents to prove that they were

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[164] *Id.* at 1234-35.

[165] *Id.* at 1236.

[166] *E.g.,* Mitchell v. Gencorp Inc., 165 F.3d 778, 781 (10th Cir. 1999) ("a plaintiff must prove level of the exposure using techniques subject to objective, independent validation ...."); Wright v. Willamette Industries, Inc., 91 F.3d 1105, 1107 (8th Cir. 1997) (same).

[167] *E.g.*, Shudel v. General Electric, 120 F.3d 991, 997 (9th Cir. 1997); Mitchell v. Gencorp, 165 F.3d at 781; Sutera v. Perrier Group of America, Inc., 986 F. Supp. 655, 662 (D. Mass. 1997). *See also* Decaprio, *supra* note 6, at 1842 (plaintiffs "typically introduce indirect measures, such as ambient air or other environmental media analyses, job and process descriptions, or chemical usage and disposal records a evidence for significant exposure. Defense counsel generally challenges such evidence as unreliable, nonspecific, or incidental to the disease in question.").

[168] *E.g.,* Dombrowski v. Gould Electronics, Inc., 85 F. Supp.2d. 456, 476 (M.D. Pa. 2000); Rhilinger v. Jancsics, 1998 WL 1182058, No. 93223 *5-8 (Mass. Super., Jan. 6, 1998).

exposed to sufficient radiation doses from the TMI nuclear accident to cause their cancer.[169] The plaintiffs lacked direct measurements of radiation levels or exposure modeling data that were sufficient to demonstrate significant radiation exposure.[170] They attempted to show significant radiation exposure based on an increased frequency of a chromosome aberration known as a "dicentric chromosome" in the plaintiffs' lymphocytes, which served as a biomarker of radiation exposure.[171] The Court of Appeals endorsed in principle the use of such biomarkers as a both a qualitative and quantitative "biological dosimeter" of exposure: "counting the number of dicentrics is an accepted method, not simply for determining if the subject of the analysis was irradiated, but also for estimating radiation dose to the individual."[172]

The court also found, however, that dicentric chromosomes are unstable, and therefore can only provide an accurate indicator of dose within one or two years of exposure, not fifteen years after exposure as was the case in the TMI litigation.[173] Moreover, both the defendants' and plaintiffs' experts agreed that an alternative cytogenetic biomarker – chromosome translocations measured by the "FISH" (Fluorescent In Situ Hybridization") method[174] – was a better biomarker of radiation exposure that remained

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[169] In re TMI Litigation, 193 F.3d 613, 622 (3d Cir. 1999), *cert. denied*, 120 S.Ct. 2238 (2000).

[170] *Id.* at 659-662, 666-683.

[171] *Id.* at 688. "Dicentric" chromosome contain two centromeres rather than the normal one, and are formed as a result of chromosome breakage. *Id.* at 688 n.24.

[172] *Id.* at 690.

[173] *Id.* at 692. The court concluded that "[r]adiation dose estimation based on dicentric enumeration is a valid and reliable scientific methodology, but the validity and reliability decrease as the time gap between the alleged irradiation and the dicentric count increases." *Id.*

[174] Chromosome translocations occur when two or more chromosomes break and rejoin to produce an interchange of chromosomal segments. *Id.* at 688 n.124. The FISH technique involves

stable long after the exposure occurred.[175] Unfortunately for the TMI plaintiffs, they attempted to introduce cytogenetic biomarkers of exposure using the FISH technique only after the deadline for new evidence had passed.[176] Both the dicentric and FISH biomarker evidence were thus excluded, the first as unreliable and the second as untimely, resulting in summary judgment for defendants.[177] Notwithstanding the adverse result for the plaintiffs in that litigation, the court's holding provides strong endorsement of the appropriate use of cytogenetic biomarkers for demonstrating and quantifying exposure.

Cytogenetic and other types of biomarkers are likely to be increasingly relied on to demonstrate exposure in future toxic injury litigation. One technique with much potential is the characterization of mutational fingerprints that are characteristic of a specific toxic substance.[178] Assays that detect such mutations can provide compelling evidence of exposure to that substance.[179] At least one testing company has already established a service to assist potential plaintiffs to establish that toxic exposures were responsible for genetic damage. Benchmark Genetics™ offers to collect and archive DNA samples from

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differential staining with flourescent dyes of DNA strands that can be used to identify chromosomes containing a translocation. *Id.* at 691 n.127.

[175] *Id.* at 692-93.

[176] *Id.* at 717-18.

[177] *Id.* at 692-93, 722.

[178] *See supra* note 38 and accompanying text

[179] Barry B. Cepelewicz & Eric Watt Wiechmann, *Genetic Injury in Toxic Tort Cases: What Science Can and Cannot Prove*, 62 DEF. COUNS. J. 201 (1995). While such mutations may provide a reliable indicator of exposure, it may be difficult to estimate risk based on such markers because it would be uncertain how common the mutations detected in one or a few somatic cells are in the billions of other human cells in which a tumor might be initiated. *Id.* at 208.

persons concerned about exposure to hazardous substances for the purpose of establishing a "genetic benchmark" that serves as a pre-exposure baseline that can be used in litigation for demonstrating subsequent genetic changes.[180]

4. Alternative Causation: Different Exposure Was Cause

A common defense strategy in toxic injury litigation is to investigate and allege other possible causes of the plaintiff's injury.[181] This defense is known as alternative causation. The availability of a broad range of validated biomarkers will greatly enhance the availability and potential success of alternative causation defenses. Testing a plaintiff for the presence of a chemical-specific biomarker of exposure or effect may provide objective confirmation of suspected alternative exposures that may not be revealed in a plaintiff's deposition or medical records.

A defendant corporation successfully used a biomarker of exposure to defend against liability in a case in which the family of a deceased worker alleged that occupational exposure to benzene caused the worker's acute myelogenous leukemia ("AML"). While it was undisputed that benzene is capable of causing AML, the jury delivered a verdict for defendant after its expert testified that benzene only causes AML with specific cytogenetic markers -- breaks in the fifth and seventh chromosomes -- which

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[180]http://www/benchmarkgentics.com. The company charges $50 for the storage of DNA samples. The company's materials advertise that "[b]y establishing a genetic benchmark now, if you ever become ill you can have comparative DNA studies to demonstrate that the genetic damage was not present prior to exposure. This information could be critical in establishing workers' compensation or liability issues." *Id.*

[181]*See* C. Ashley Royal, *The Defense of Medical Causation*, TRIAL, Oct. 1987, at 40, 42 ("A valid alternative explanation of causation provides the surest basis for a verdict for the defendant."); James G. McConnell, *Alternative Causation: The Best Defense is a Good Offense*, TOXICS LAW REP. (BNA), June 14, 1989, at 51.

were not present in the worker's DNA.[182] A few weeks later, a West Virginia trial court rejected the identical defense in another case involving benzene and AML, with the court finding the defendant experts' cytogenetic marker theory "nothing more than an untested, unsupported hypothesis cloaked in the aura of scientific knowledge."[183] A Florida federal district court also rejected the same defense on scientific reliability grounds in another subsequent case.[184]

While some scientific evidence indicates that chromosomes five and seven are selectively altered by benzene exposure,[185] and that these chromosome aberrations are associated with AML,[186] the available evidence does not suggest that all or even most AML cases caused by benzene are associated with breaks in these two chromosomes.[187] At best then, the absence of aberrations in chromosomes five and seven may reduce somewhat, but not altogether, the possibility that benzene was the causative agent. The

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[182]*See Expert Testimony: Jury Returns Verdict for Oil Company After Testimony on Missing Disease Marker*, CHEM. REG. REP. (BNA), April 24, 1998 (reporting jury verdict in Wells v. Shell Oil Co., DCE Texas, jury verdict 3/2/98).

[183]*See Benzene: Defense Experts' Opinions Inadmissible, Not Based on Reliable Methodology*, CHEM REG. REP. (BNA), June 26, 1998 (discussing decision in Lavender v. Bayer Corp., W. Va. Cir. Ct., No. 93-C-226-K, 5/29/98).

[184]Edwards v. Safety-Kleen Corp., 61 F. Supp.2d 1354, 1359-60 (S.D. Fla. 1999).

[185]Wayne S. Stilklman, Marileila Varella-Garcia & Richard D. Irons, *The Benzene Metabolite, Hydroquinone, Selectively Induces 5q31- and -7 in Human $CD34^+CD19^-$ Bone Marrow Cells*, 28 EXPERIMENTAL HEMATOLOGY 169 (2000).

[186]S.A. Narod & I.D. Dube, *Occupational History and Involvement of Chromosomes 5 and 7 in Acute Nonlymphocytic Leukemia,* 38 CANCER GENET. CYTOGENET. 261 (1989); L.P. Zhang, *et al., Increased Aneusomy and Long Arm Deletion of Chromosomes 5 and 7 in the Lymphocytes of Chinese Workers Exposed to Benzene*, 19 CARCINOGENESIS 1955 (1998).

[187]*See* M.T. Smith & L. Zhang, *Biomarkers of Leukemia Risk: Benzene as a Model*, 106 (Suppl. 4) ENVTL. HEALTH PERSPECT, 937, 941 (1998).

attempts by defendants to argue that the absence of chromosome five and seven aberrations positively excludes benzene as the cause of a plaintiff's leukemia demonstrates once again that litigants are prone to exaggerate the significance of biomarkers, and at least some courts and juries are likely to be misled by such arguments.

5. *Alternative Causation: Genetics Was Cause*

A defendant may also base an alternative causation defense on evidence that the plaintiff's injuries were caused solely by a pre-existing genetic condition rather than defendant's actions.[188] For example, the plaintiff may carry an inherited mutation that puts the plaintiff at an increased risk of developing cancer spontaneously.[189] Even before the advent of widespread genetic testing, defense counsel aggressively seek information on plaintiffs' genetic background in order to support a potential alternative causation defense.[190] One genetics expert has advised that defendants should undertake a "genetic workup" of the

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[188]All diseases result from an interaction of exogenous (e.g., environmental exposures) and endogenous factors (e.g., genetic and other susceptibilities). *See* Kenneth J. Rothman, Modern Epidemiology 14 (1986) ("it is easy to show that 100 percent of any disease is environmentally caused, and 100 percent is inherited as well."). The tort system has traditionally attempted to separate out and assign causation to discrete factors, and until now this task has been complicated primarily by the numerous exogenous factors that contribute in some way to an injury or disease. *See, e.g.,* Parascandola, *supra* note 137, at 37; Guido Calabresi, *Concerning Cause and the Law of Torts: An Essay for Harry Kalven, Jr.*, 43 U. CHI. L. REV. 69, 71 (1975) ("Obviously there are an infinite number of acts or activities that are causally linked to every injury."). The task of identifying legal causes will become even more complicated in the future as genetic variables affecting individual susceptibility are understood, thus offering a genetic component in the causation of every disease. *See id.* at 106 ("the prospect of genetic engineering has again changed the causal language appropriate to this disease. Now one can, in a meaningful way, speak of a genetic predisposition as a 'cause' of tuberculosis.").

[189]Ellinger, *supra* note 6, at 64.

[190]McConnell, *supra* note 181, at 53 ("It is important to learn as much as possible about the genetic background of a plaintiff.").

plaintiff in *every* case involving developmental disabilities.[191]

Defendants have frequently attempted to argue alternative causation defense based on heritable disorders. To date, most of these attempts have been based on speculation rather than objective data, and have been rejected by courts on that ground.[192] In at least one case, the defendant's genetic causation defense was defeated after genetic testing of plaintiff disproved the defendant's theory.[193] In a few cases, however, defendant's genetic causation theory was successful.[194] In other cases, the testimony of plaintiffs' expert on causation was ruled inadmissible for failure to exclude genetics as a possible cause when defendant had identified potential genetic causes of the relevant disease.[195]

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[191]Van Voris, *supra* note 6, at A1 (quoting Dr. Philip R. Reilly).

[192]*E.g.,* Dombrowski v. Gould Electronics, 85 F. Supp.2d. 456, 477 (M.D. Pa. Feb. 3, 2000) ("There is a distinct lack of credible testimony ... showing that genetics or family environments did, in fact cause the difficulties suffered by these individual Plaintiffs."); Willey v. Ketterer, 869 F.2d 648 (1st Cir. 1989) (defendant's argument that genetic predisposition caused plaintiff's cerebral palsy rather than medical malpractice was not supported by valid evidence and hence prejudicial to jury); Matthews v. Secretary of Dep't of Health and Human Servs., 18 Cl. Ct. 514, 523 (1989) (government's argument that child's illness and death were caused by genetic disease rather than vaccine rejected as purely speculative and lacking any evidentiary support).

[193] Gess v. U.S., 991 F. Supp. 1332, 1364 n.29 (M.D. Ala. 1997).

[194]*E.g.*, Wintz v. Northrop Corp., 110 F.3d 508, 511-12 (7th Cir. 1997) (summary judgment for defendant after undisputed evidence showed that child suffered from genetic disorder that "almost certainly" caused her health problems); Vant Erve v. Secretary of Health & Human Services, 43 Fed. Cl. 338, 345-46 (1999), *aff'd*, 2000 WL 425005 (Fed. Cir., Apr. 18, 2000) (accepting government's genetic causation defense even though the alleged unidentified genetic disorder was, according to plaintiff, "idiopathic, unexplained, unknown, hypothetical and undocumented.").

[195]*E.g.,* National Bank of Commerce v. Dow Chemical Co., 965 F. Supp. 1490, 1520-23 (E.D. Ark. 1996); Rodriguez v. Cigna Property & Casualty Co., 956 F. Supp. 544, 549, 552 (M.D. Pa. 1996); Lofgren v. Motorola, 1998 WL 299925 *33 (Ariz. Super. June 1, 1998).

In one frequently discussed case, a mother filed suit on behalf of her 13-year old mentally retarded son against the manufacturer of solvents to which the mother was occupationally exposed while pregnant and which allegedly caused the child's condition.[196] Defendant argued that the son's medical symptoms suggested that his retardation resulted from an inherited genetic defect (known as "fragile X" syndrome[197]) rather than from prenatal solvent exposure.[198] Defendant sought permission to genetically test the son, which the court granted over plaintiff's objections.[199] However, when the time came to take a blood sample for the genetic test, the son, who was then thirteen years old but purportedly terrified of needles, resisted the procedure so violently that the administering physician discontinued the blood test before a sample could be taken.[200] In a subsequent meeting between the parties' counsel and the judge, plaintiff's counsel revealed that the mother had subsequently been genetically tested and the results were allegedly inconsistent with the child having "fragile X" syndrome, although the test results were never

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[196]*See* Sally Lehrman, *Pushing Limits of DNA Testing: Suit Prompts Study Into Whether a Birth Defect Was Inherited or Caused by Toxics*, S.F. EXAMINER, June 5, 1994, at A1 (discussing case of Severson v. KTI Chemicals Inc.); Meg Fletcher, *Genetic Testing Ordered in Product Liability Case*, BUSINESS INSURANCE, Aug. 1, 1994 (same).

[197]Fragile X syndrome is an inherited condition characterized by a group of physical and behavioral symptoms, and which is caused by a gene on the X chromosome. Because males receive their only copy of the X chromosome from their mother, a son with Fragile X syndrome inherited the condition from his mother, even though the mother may have not have the condition because of a normal gene on her second X chromosome. *See* The National Fragile X Foundation, *What is Fragile X?*, http://www.nfxf.org (visited June 12, 2000).

[198] *See* Lehrman, *supra* note 196; Fletcher, *supra* note 196.

[199]Lehrman, *supra* note 196; Fletcher, *supra* note 196.

[200]Personal communication with Kevin Mayer, counsel for defendant, April 7, 2000. Today, genetic tests could be administered in a less intrusive or painful manner, such as by taking a buccal swab (from inside the mouth).

provided to the defendant or the court.[201] The genetic testing issue was put to the side while issues other than causation were first litigated in a bifurcated trial, and after a decision on those issues in favor of plaintiff, the case settled.[202]

This example shows that a genetic evidence can play a critical role in litigating causation. In this case, if the genetic test had been conducted and supported the defendant's argument that the boy suffered from the genetic condition alleged, the results would have provided powerful if not conclusive support for defendant's case.[203] Alternatively, where, as apparently occurred here, plaintiff is able to offer genetic evidence refuting a potential genetic cause of the injury at issue, it will weaken the defendant's case and may facilitate a favorable settlement for the plaintiff.

C. Damages

1. Plaintiff Would Have Developed Same Condition Inevitably

As discussed above, it is unclear whether a defendant would be liable for causing the development of disease in a plaintiff genetically predisposed to such a condition.[204] Even if a defendant is held liable, however, the defendant can reduce its damages payable if it can show that the plaintiff's injury eventually would have developed even in the absence of defendant's conduct. Courts have often discounted

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[201] *Id.*

[202] *Id.*

[203] Plaintiff argued in the *KTI* case that more than 13 percent of boys with the fragile X genetic marker show no mental retardation, and thus even if the boy had tested positive for fragile X syndrome, that evidence would not have been conclusive that the genetic marker was the cause of the boy's mental retardation. *See* Lehrman, *supra* note 196.

[204] *See supra* notes 67-97 and accompanying text.

damages to account for the likelihood that a plaintiff's latent tendency or asymptomatic pre-existing condition would likely have inevitably resulted in disease.[205] Thus, if a defendant can show that a genetically susceptible plaintiff likely would have developed the same condition without defendant's actions, the damages for which defendant is liable should be discounted accordingly. Of course, because the likelihood, timing, and severity of disease progression from almost any genetic predisposition is probabilistic rather than deterministic, courts will be challenged to calculate the appropriate factor by which to discount damages.[206]

2. *Plaintiff Has Diminished Life Expectancy*

A further extension of the concept discussed in the previous subsection, whereby damages are discounted if the plaintiff was genetically predisposed to developing the *same* condition, would be to also discount damages if the plaintiff was predisposed to some other genetically-influenced condition that shortens life expectancy.[207] Defendants who have been held liable for a plaintiff's injury have been able to reduce damages by introducing evidence of plaintiff's diminished life expectancy due to factors such as

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[205] *E.g.,* Sauer v. Burlington Northern Rd. Co., 106 F.3d 1490, 1495 (10th Cir. 1996); Steinhauser v. Hertz Corp., 421 F.2d 1169, 1170-71 (2d Cir. 1970); Kegel v. United States, 289 F. Supp. 790 (D. Mont. 1968); Stoleson v. U.S., 708 F.2d 1217, 1223 (7th Cir. 1983); Henderson v. United States, 328 F.2d 502, 504 (5th Cir. 1964); Holladay v. Chicago, Burlington & Quincy Rd. Co., 255 F. Supp. 879, 886-87 (S.D. Iowa 1966).

[206] Thirty years ago, one court faced with the problem of discounting damages because of plaintiff's predisposition remarked that "[i]t is no answer that exact prediction of [the plaintiff's] future apart from the accident is difficult or even impossible," because "[h]owever taxing such a problem may be for men who have devoted their lives to psychiatry, it is one for which a jury is ideally suited." Steinhauser v. Hertz Corp., 421 F.2d 1169, 1174 (2d Cir. 1970). Such confidence in a jury's capability to calculate an appropriate discount factor for a genetically predisposed plaintiff would be unlikely today.

[207] *See* Mark A. Rothstein, *Preventing the Discovery of Plaintiff Genetic Profiles by Seeking to Limit Damages in Personal Injury Litigation*, 71 IND. L.J. 877 (1996).

cancer, heart disease, or the use of tobacco, drugs or alcohol.[208] Recently, some courts have ordered the plaintiff to undergo AIDS testing or to disclose the results of previous such tests for the purpose of determining life expectancy for awarding damages.[209] A defendant could likewise rely on a genetic test result showing that the plaintiff is predisposed to developing a late-onset life-threatening disease that will shorten her remaining lifespan, thereby reducing a damage award.[210] Conversely, a plaintiff with a healthy genetic diagnosis could play the other side of the coin – arguing that her genetic well-being extends her expected lifespan, thus justifying a corresponding increase in damages.[211]

Some commentators argue that genetic predictors of life-shortening illness (or life-extending healthy prognosis) are too speculative and irrelevant to meet the standards for admissibility.[212] The date of onset of the future genetic disease is uncertain, and most genetic conditions have variable penetrance and expression, creating substantial uncertainty about the appearance and severity of the predicted disease.[213]

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[208] *Id.* at 886; Niccol Kording & Janine P. DuMontelle, *An Overview of Admissibility of Genetic Test Results in Federal Civil Actions: An Uncertain Destiny*, 19 WHITTIER L. REV. 681, 701 (1998).

[209] Pettyjohn v. Goodyear Tire & Rubber Co., 1992 WL 105162 (E.D. Pa. April 29, 1992) (ordering HIV testing); Agosto v. Trusswal Systems Corp., 142 F.R.D. 118 (E.D. Pa. 1992) (ordering disclosure of HIV test results). *See also* Anthony S. Niedwiecki, *Science Fact or Science Fiction? The Implications of Court-Ordered Genetic Testing Under Rule 35*, 34 U. SAN. FRANCISCO L. REV. 295 (2000) (discussing court-ordered HIV and genetic testing).

[210] Rothstein, *supra* note 207, at 879 ("Conceivably, in every case in which the plaintiff seeks to recover for permanent or long-term disability or lost future earnings, ... the defendant could seek to discover the plaintiff's risk of premature incapacity or mortality by obtaining genetic records or performing genetic testing.").

[211] Kording & DuMontelle, *supra* note 208, at 702.

[212] *Id.* at 690-91.

[213] *See* Rothstein, *supra* note 207, at 882; Kording & DuMontelle, *supra* note 208, at 690-91.

However, other predictors that are routinely admitted for the purpose of proving damages – such as smoking behavior – are arguably no less speculative or relevant.[214] Commentators have also suggested that the sensitive nature of genetic information makes it distinct from other types of health information, and therefore courts or legislatures should preclude genetic testing of plaintiffs for the specific purpose of determining life expectancy.[215]

III. POLICY AND NORMATIVE ISSUES

The many existing and potential applications of biomarkers in toxic injury litigation discussed above offer much promise in making the tort system more informed, objective and fair. Yet, at the same time these technologies portend practical benefits to the tort system, many of the potential applications of biomarkers raise complex or even troubling policy and normative issues. While a full exposition of those issues is not possible here, some are briefly canvassed below.

A. Consistency with Substantive Objectives of Tort Law

The primary objectives of tort law are generally categorized into fairness and utility goals.[216] Fairness considerations, often discussed under the rubric of "corrective justice,"[217] include providing

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[214] *But see* Kording & DuMontelle, *supra* note 208, at 701 (arguing that genetic test results are more remote and speculative than other factors for determining life expectancy).

[215] Rothstein, *supra* note 207, at 893-94; Ronald M. Green & A. Mathew Thomas, *DNA: Five Distinguishing Features for Policy Analysis*, 11 HARV. J. L. & TECH. 571 (1998).

[216] *E.g.*, George P. Fletcher, *Fairness and Utility in Tort Theory*, 85 HARV. L. REV. 537 (1972).

[217] One formulation of the term "corrective justice" is that "as a matter of individual justice between the plaintiff and the defendant, the defendant who has caused an injury to the plaintiff in violation of his rights in his person or property must compensate him for such injury, whether or not imposition of liability will further some collective social goal." Richard W. Wright, *Actual Causation v. Probabilistic Linkage: The Bane of Economic Analysis*, 14 J. LEGAL STUDIES 435, 435 (1985). *See also* Kenneth W. Simons,

compensation for injured persons and penalizing actors who cause such injuries.[218] Utility or instrumental goals include imposing an optimal level of deterrence on risk-creating activities and efficiently allocating or "spreading" the costs of accidents.[219] The use of biomarkers for the purpose of adjudicating causation can enhance both the fairness and utility objectives of tort law. Biomarkers can provide additional probative information on whether a defendant's conduct did or did not cause or contribute to the plaintiff's injury. In much the same way that forensic DNA evidence has helped both to identify criminals and exonerate the innocent,[220] biomarkers can help to prove causation for toxic substances that injure plaintiffs, as well as to vindicate a product where no causation exists. As such, these biomarker applications enhance corrective justice by improving the likelihood of recovery for, as well as restricting recovery to, those plaintiffs that have truly been injured by defendant's actions. Likewise, from an instrumental perspective, the use of biomarkers to demonstrate or rebut causation may contribute to optimal deterrence by requiring defendants to pay appropriate damages for every person they injure, but only those people.

The potential use of biomarkers to expand or contract the scope of liability raises more difficult issues under both the fairness and instrumental strands of tort objectives. Take for example the argument that plaintiffs genetically susceptible to a product should not be entitled to compensation.[221]

Collective Justice and Liability for Risk-Creation: A Comment, 38 UCLA L. REV. 113, 125-26 (1990) (listing various definitions of corrective justice).

[218] Fletcher, *supra* note 216, at 543-557.

[219] *See generally* WILLIAM M. LANDES & RICHARD A. POSNER, THE ECONOMIC STRUCTURE OF TORT LAW (1987).

[220] *See supra* note 4.

[221] *See supra* notes 67-97 and accompanying text.

Corrective justice has two distinct fairness prongs: (i) whether the plaintiff is deserving of compensation; and (ii) whether the defendant's conduct warrants imposition of liability.[222] Both prongs are debatable in the case of a defense based on genetic susceptibility. If such a defense were recognized, more injured plaintiffs will not recover for their injuries resulting at least in part from defendants' conduct, seemingly inconsistent with the fairness objectives of corrective justice.[223] Yet, as some courts have argued, an individual's unusual susceptibility might more properly be viewed as the primary cause of the adverse effect in such contexts,[224] in which case perhaps that plaintiff is not entitled to compensation from the tort system, anymore than someone who is stricken with a heart attack or spontaneous cancer. Turning to the defendant's conduct, it may be unfair to hold liable a defendant who did not, and could not, know of the risk to hyper-susceptible individuals.[225] Conversely, some argue that defendant should be held responsible when it injures any person no matter how susceptible, and thus it would be unfair for "biological attributes of the victim [to] determine the blameworthiness of the actor."[226]

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[222]Fletcher, *supra* note 216, at 540 ("if the victim is entitled to recover by virtue of the risk to which he was exposed, there is an additional question of fairness in holding the risk-creator liable for the loss."). *But see* Weinrib, *supra* note 94, at 431 (defendant's wrongdoing and causation of plaintiff's injuries are not independent notions but rather are "symmetrically related").

[223]The plaintiff's reasonable expectations in a safe product have been disappointed, and even though the defendant may not have been blameworthy if the susceptibility was not foreseen, the defendant profited from the sale of the product. *See* Henderson, *supra* note 75, at 785-787.

[224]*See supra* note 77 and accompanying text.

[225]Fletcher, *supra* note 216, at 541 (fairness may weigh in favor of excusing a defendant who could not have known of the risk latent in his conduct); Schroeder, *supra* note 104, at 451-460 (dominant view is to evaluate the moral character of the defendant's actions *ex ante*).

[226]Rochelle Cooper Dreyfuss and Dorothy Nelkin, *The Jurisprudence of Genetics*, 45 VAND. L. REV. 313, 327 (1992).

The instrumental merits of exempting or limiting liability for genetically susceptible individuals are also difficult to evaluate. Cost allocation goals would appear to weigh in favor of imposing liability on the defendant, because it can spread the costs over all users of the product, and lead to optimal levels of use and consumption.[227] While neither the defendant nor plaintiff may have anticipated the idiosyncratic response, the defendant may be in the best position to conduct research and to identify genetic susceptibilities to its products, which likewise suggests placing the liability on the defendant.[228] It has also been argued that allowing defendants to use the susceptibility of plaintiffs as a defense to liability will reduce deterrence to below optimal levels.[229] On the other hand, as genetic knowledge and testing becomes more widespread, individual plaintiffs may be in the best position to discover their own susceptibilities, and accordingly should absorb the loss.[230] As to deterrence arguments, if the defendant is unable to target special protection for the genetically susceptible, then to avoid liability for such persons it would be required to provide the entire group with the extra margin of protection needed to protect the most susceptible,

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[227]*See* Henderson, *supra* note 75, at 785-86.

[228]*See* Guido Calabresi & Kenneth C. Bass, *Right Approach, Wrong Implications: A Critique of McKean on Products Liability*, 38 U. CHI. L. REV. 74, 87 (1970) ("To the extent that [susceptible] potential victims could not individualize their greater risk, the cheapest cost avoidance would probably lie in the development of a compound that did not have the danger or in a test to indicate who was susceptible.").

[229]LANDES & POSNER, *supra* note 219, at 250 ("If people with above-average susceptibility to injury were never allowed to recover full damages for the negligent injuries inflicted on them, the expected liability costs to potential injurers would be below the actual injury costs."); Dreyfuss and Nelkin, *supra* note 226, at 328 n.90 (arguing that a defendant, lacking ex ante knowledge of who is susceptible, will reduce the overall total level of care if not held liable for genetically susceptible individuals, thus resulting in less protection for each person in the population).

[230]*See* Calabresi & Bass, *supra* note 228, at 86 (unusually susceptible plaintiff may be in best position to avoid harmful exposure).

perhaps resulting in excessive protection and over-deterrence overall. Finally, it may be unduly burdensome or not cost-effective to expect defendants to try to anticipate and prevent every possible idiosyncratic response in the population.[231]

Another potential application of biomarkers that raises difficult doctrinal issues is the use of biomarkers of effect to substantiate, and thus make more common and successful, claims based on latent risks.[232] One torts theorist has described the issue of liability for risk exposure "the most problematic area of current tort practice."[233] This issue is likely to become even more problematic and pressing with the availability of biomarkers to identify and quantify widespread latent risks in an objective manner.[234] Some commentators have argued that both the fairness and utility objectives of tort law would be enhanced by shifting to liability based on risk.[235] For example, it is argued on fairness grounds that the culpable act of a defendant is its unilateral imposition of an unreasonable risk on the victim, not the fortuitous event of whether that risk-creating act happens to manifest into an injury in that particular case or not.[236] Similarly, from an instrumental perspective, risk compensation may provide a more effective deterrent by directly focusing on

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[231]*See* Henderson, *supra* note 75, at 803-04.

[232]*See supra* notes 99-125 and accompanying text.

[233]Wright, *supra* note 149, at 1067.

[234]*See* Kanner, *supra* note 6, at 356 (latent risks supported by "demonstrable scientific facts" will increase salience of legal claims for such risks).

[235]*E.g.,* Schroeder, *supra* note 104; Robinson, *supra* note 106, at 783; Rosenberg, *supra* note 131, at 885-86; David Gerecke, *Risk Exposure as Injury: Alleviating the Injustice of Tort Causation Rules*, 35 McGill L. J. 797, 806-811 (1990).

[236]Schroeder, *supra* note 104, at 465.

the conduct we wish to deter (risk-creation) rather than the consequence of that conduct (the resultant injury).[237]

Compelling arguments can also be advanced against a more widespread cause of action for latent risks. Injury is the very essence of corrective justice, because a defendant's duty to compensate the plaintiff arises only in the context of redressing an injury to the plaintiff's body or interests caused by that defendant.[238] If there is no injury, the plaintiff is in no need of compensation.[239] Similarly, from an instrumental perspective, social utility may not be maximized by litigating risk-creation independent of injury, as the transaction costs of such litigation could be enormous. These and no doubt many other doctrinal and substantive policy issues will be presented or intensified by the widespread utilization of biomarkers in tort litigation.

2. Process and Procedural Considerations

To the extent that biomarkers provide valid, objective quantitative evidence of exposure or

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[237] *Id.* at 465-66; Gerecke, *supra* note 235, at 808.

[238] *E.g.*, Wright, *supra* note 217, at 437-39; Stephen R. Perry, *Risk, Harm, and Responsibility*, in PHILOSOPHICAL FOUNDATIONS OF TORT LAW (ed. David G. Owen, 1995), at 321, 330-39.

[239] Of course, it could be argued that the imposition of risk is an injury to a person's interests. *See* Gerecke, *supra* note 235, at 810 ("The injury is exposure to the risk."). Yet, risk -- defined as the probability of an adverse event multiplied by the consequences of that adverse event -- is a contingency - it may or may not manifest into the adverse event. In some cases, the risk will not manifest, in which case we can conclude *post hoc* that this particular risk event has not made the person any worse off (except perhaps for any psychological pain and fear experienced, or need for increased medical monitoring). Under this view, risk is not itself an injury, it only becomes an injury when the risk becomes manifest as disease. *See* Perry, *supra* note 238, at 321 ("risk does not ... constitute harm in itself.").

risk, they may reduce the indeterminancy that currently plagues toxic injury litigation.[240] On the other hand, the widespread use of biomarkers will present new, or exacerbate existing, problems in adjudicating toxic injury cases. Because the information provided by biomarkers is almost always probabilistic rather than deterministic, biomarker evidence will further strain the statistical acumen of judges and juries.[241] Moreover, given the one-shot nature and enormous stakes in toxic injury litigation, litigants are unlikely to wait for full validation of promising new biomarker evidence that could be helpful to their case.[242] Indeed, both plaintiffs and defendants have already made exaggerated or premature claims for biomarkers in some cases.[243] Courts will be challenged to carefully evaluate proffered biomarker evidence under both the reliability and relevance prongs of *Daubert*.[244]

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[240]As one federal district court lamented, "[c]urrent medical science cannot state whether or how exposure to toxic substances affects individuals. It cannot yet detect the present effect of the exposure, and, therefore, it cannot supply to the legal system information concerning the nature of present injury or of causation. In the absence of that information, the legal system now struggles to adapt." Barth v. Firestone Tire & Rubber Co., 661 F. Supp. 193, 196 (N.D. Cal. 1987)

[241]*Cf.* Troyen A. Brennan, *Untangling Causation Issues in Law and Medicine: Hazardous Substances Litigation*, 107 ANNALS. INTERNAL MED. 741, 745 (1987) ("judges, juries, and lawyers are confused by probabilistic evidence of causation in hazardous substance litigation.").

[242]An example of the tendency for premature reliance on novel scientific evidence is provided by the proliferation in the 1980s of immunotoxicity claims – sometimes referred to as "clinical ecology" or "chemically induced immune dysfunction" – which purported to be supported by various "objective" diagnostic tests, but which often lacked a valid scientific basis. *See, e.g.,* Eliot Marshall, *Immune System Theories on Trial*, 234 SCIENCE 1490 (1986).

[243]*See supra* notes 153-162, 183-187 and accompanying text.

[244]The U.S. Supreme Court in *Daubert* identified two prongs of analysis that govern the admission of expert scientific testimony, with the first prong evaluating the "reliability" or scientific validity of the testimony, and the second prong evaluating the relevance or "fit" of the testimony. Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 590-91 (1993).

Another concern, similar to that raised in the earlier case law and commentary on the use of DNA evidence in criminal cases, is that jurors may give too much weight to genetic testing results.[245] Some commentators have similarly argued that the use of genetic biomarkers in tort litigation will contribute to the reductionist tendency to over-emphasize biological and genetic factors to explain disease and behavior, described as "genetic essentialism."[246] Notwithstanding the legitimacy of these criticisms in many respects, it is also true that the relevancy of genes and other biomarkers to our understanding of the body's response to toxic substances continues to grow with advancing scientific knowledge.[247] The tort system would ignore this important information at its peril.

C. Plaintiff Confidentiality and Privacy

The many potential uses of biomarkers will often involve genetic or other testing of plaintiffs, or the disclosure of records from any previously conducted testing. Rule 35 of the Federal Rules of Civil Procedure, as well as equivalent rules under the law of most states, may require a party to litigation to submit to medical testing upon a showing of good cause.[248] Courts generally hold that by filing litigation to recover

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[245]*See* Kording & DuMontelle, *supra* note 208, at 704. *See also* Willey v. Ketterer, 869 F.2d 648, 650 (1st Cir. 1989) (defendant's unsupported references to possible genetic predisposition of plaintiff found to be prejudicial to jury).

[246]Dreyfuss & Nelkin, *supra* note 226, at 320-21; Jennifer Wriggins, *Genetics, IQ, Determinism, and Torts: The Example of Discovery in Lead Exposure Litigation*, 77 BOSTON U. L. REV. 1025, 1034-39 (1997).

[247]*E.g.*, WEINBERG, *supra* note 123, at 151 ("Cancer is a disease of damaged genes."); Eric R. Fearon, *Human Cancer Syndromes: Clues to the Origin and Nature of Cancer*, 278 Science 1043, 1043 (1997) ("Cancer is a genetic disease...."); Schulte, *supra* note 43, at 439 ("All medicine is moving toward a molecular understanding of disease.").

[248]*See* Rothstein, *supra* note 207, at 889-91; Niedwiecki, *supra* note 209, at 299-309.

for bodily injuries, a plaintiff has put her medical condition "in controversy."[249] Adhering to this view, several courts have already ordered genetic testing of plaintiffs in tort cases.[250]

Court-ordered genetic testing may threaten privacy and other rights of plaintiffs. A plaintiff may not wish to know certain facts about her own genetic make-up, as the results of genetic testing can have a substantial and in some cases devastating psychological impact on at-risk individuals.[251] A plaintiff may also be concerned that the testing information could be disclosed to third parties and misused by insurers or employers.

These potential threats cannot be taken lightly. A plaintiff's genetic data is among the most private and sensitive personal information there is, and needs appropriate protection.[252] The National Academy of Science's Institute of Medicine affirmed the widely held bioethical principle that genetic tests should only be conducted when they are of benefit to the individual being tested.[253] On the other hand, the

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[249]*See* Rothstein, *supra* note 207, at 889-90. For example, the Supreme Court has held that by seeking to recover substantial monetary damages in a personal injury action, the plaintiff "provides the defendant with good cause for an examination to determine the existence and extent of any asserted injury." Schlagenhauf v. Holder, 379 U.S. 104 (1964).

[250]Bennett v. Fieser, 1994 WL 542089 (D. Kan. 1994) (court orders genetic testing of plaintiff in a medical malpractice case); Dodd-Anderson v. Stevens, 1993 WL 273373 (D. Kan. 1993) (same); Gess v. U.S., 991 F. Supp. 1332, 1364 n.29 (M.D. Ala. 1997) (defendant's expert conducts genetic tests on plaintiff). *See also supra* notes 196-202 and accompanying text (KTI case).

[251]*See* Green & Thomas, *supra* note 215, at 572 (referring to "informational risks" from disclosure of genetic information to self and others); Niedwiecki, *supra* note 209, at 338-41.

[252]*See generally* GENETIC SECRETS: PROTECTING PRIVACY AND CONFIDENTIALITY IN THE GENETIC ERA (Mark A. Rothestein, ed., (1997).

[253]INSTITUTE OF MEDICINE, ASSESSING GENETIC RISKS: IMPLICATIONS OF HEALTH AND SOCIAL POLICY 47 (1994); Rothstein, *supra* note 207, at 898.

use of genetic and other biomarker data may provide important benefits to *both* plaintiffs and defendants in toxic injury litigation, thus advising against a blanket prohibition on genetic testing, or prohibiting defendant from obtaining and using the same types of genetic information that the plaintiff might rely on in favorable circumstances.[254] Moreover, testing for biomarkers of exposure and effect usually will not raise the same level of privacy concerns as genetic testing. Such testing will not normally reveal the genetic background of the plaintiff, and indeed may be beneficial on public health grounds to inform plaintiffs of the nature and level of their toxic exposures, which may facilitate appropriate medical monitoring and preventive care.[255]

Several precautions can also limit the potential risks and unfairness of court-ordered genetic testing. First, any sensitive genetic or other personal information should, at plaintiffs' request, be covered by a protective order that would prevent its disclosure to third parties, such as insurers and employers.[256] Second, genetic testing should only be compelled based on an adequate showing of good cause by the defendant.[257] Third, any approved testing should be limited in scope to those specific traits or

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[254]*See* Friends of the Earth (UK), *supra* note 52, at 41-42 (genetic susceptibility screening will increase the chances of liability cases succeeding by making it easier to prove causation"); Johnson, *supra* note 6, at 370 ("the use of biological markers is hardly a requiem for toxic tort litigation–it may well engender more."); ASHFORD *et al.*, *supra* note 6, at 156-58 (discussing promise of biomarkers to assist tort recovery for injuries from toxic exposures).

[255]Biomarkers of effect may nevertheless reveal some sensitive information about future disease that the plaintiff may not want to know or which she may not want family members or third parties such as insurers or employers to know.

[256]*But see* Niedwiecki, *supra* note 209, at 345-46 (noting deficiencies of protective order to protect genetic tests from insurers who ask plaintiff about any existing genetic testing data).

[257]Courts can protect plaintiffs' interests against overly intrusive or non-essential personal discovery by case-by-case discretionary review of such discovery requests. *See, e.g.,* Andon v. 302-304 Mott St. Assoc., __ N.E.2d __, 2000 WL 571672 (N.Y. May 11, 2000) (refusing to allow discovery of maternal IQ in lead poisoning case because the burden of subjecting the plaintiff's mother to such testing would

predispositions for which defendant has demonstrated good cause.[258] Fourth, to the extent possible, plaintiffs should be shielded from receiving genetic information that they do not want to know.[259]

Conclusion

While certainly not a panacea, biomarkers of exposure, effect and susceptibility have many potential beneficial applications for both plaintiffs and defendants in toxic injury litigation. For many of these potential applications, especially those related to proving or disproving causation, doctrinal templates already exist for the use of biomarker evidence, and biomarkers offer the potential to substantially improve the resolution of the vexing causation issues in toxic injury litigation. Other potential applications of biomarkers, such as in supporting a genetic susceptibility defense or causes of action based on latent risk, present more difficult doctrinal quandaries. Many potential applications of biomarkers will also present difficult but not insurmountable problems relating to reliability and personal privacy. Notwithstanding the many concerns

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outweigh any relevance to the causation inquiry); Niedwiecki, *supra* note 209, at 338-52 (advocating "examination of the examination" approach where judges evaluate appropriateness of genetic tests on a case-by-case basis).

[258]A showing of good cause should include a demonstration that the traits for which testing is requested are relevant to outcome of the case, and that a sufficient scientific foundation (including reliability and validation) exists for use of the particular biomarker in the litigation. Some commentators have argued that genetic testing may be appropriate when it is directly relevant to causation, but should be rejected by courts when it solely for a "fishing expedition" to find some genetic predisposition not at issue in the case but only relevant to show a diminished life expectancy in the plaintiff. *See supra* notes 212-215 and accompanying text; Rothstein, *supra* note 207, at 900-01. Genetic "fishing expeditions" for the presence of late-onset genetic susceptibilities that might reduce life expectancy of the plaintiff would not only have marginal benefits, but could inflict enormous psychological harm on the plaintiff from the discovery that they are likely to develop a late onset genetic disease such as Huntington's disease. *Id.*

[259] One suggested approach is to require the testing to be performed by a neutral third party, who would only provide answers to specific questions directly relevant to the litigation, with all other information kept confidential and destroyed. *See* Ellinger, *supra* note 6, at 69-70.

and limitations, biomarkers promise to significantly transform toxic injury litigation, much sooner than most expect.[260]

[260]"Ninety-nine percent of people don't have an inkling about how fast this [genetic] revolution is coming." Steve Fodor, President of Affymetrix, a leading DNA chip manufacturer, quoted in Stipp, *supra* note 15.

Physician liability: the next big thing for personalized medicine?

Liability is likely to be a major driver for the future direction and implementation of personalized medicine, spurring the adoption of genetic tests and other pharmacogenomic technologies, in some cases appropriately, and in other cases prematurely or as inefficient defensive medicine. While all entities in the personalized medicine chain will face liability risks, physicians will be at the greatest risk owing to their lack of defenses, limited experience in dealing with genetics and the growing disparities within the profession in implementing new medical technologies. The history of liability for genetic testing, primarily in the prenatal testing context, suggests that liability will often be both unpredictable and influential in changing medical practice. It is critical to anticipate and attempt to prevent such liability risks in a proactive manner so to minimize the disruptive impact that liability can cause.

KEYWORDS: ***BRCA*** ▪ **gene-expression profiling** ▪ **genetics** ▪ **lawsuit** ▪ **liability** ▪ **litigation** ▪ **pharmacogenomics** ▪ **physician liability** ▪ **whole-genome sequencing**

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The era of personalized medicine is approaching – more slowly than many originally predicted, but nevertheless advancing in fits and starts [1]. The central concept of personalized medicine is sound – healthcare can potentially be more effective and efficient if it is personalized by targeting the genetic or molecular profile of individual patients rather than applying the traditional 'one-size-fits-all' approach to diagnosis and management. As Francis Collins, the Director of the US NIH, recently noted, "the power of the molecular approach to health and disease has steadily gained momentum over the past several decades and is now poised to catalyze a revolution in medicine" [2].

Yet, despite the promise and potential, a variety of impediments and barriers have slowed down the implementation and uptake of personalized medicine [3]. Notwithstanding a few noteworthy exceptions, there has been relatively little application of molecular profiling in the routine practice of medicine to date [1,4,5]. A number of specific challenges have been identified to the wider integration of personalized medicine into routine medical care, including: clinical usefulness and improved outcomes will need to be demonstrated; tests will need to be validated and their costs will need to come down; payers will need to reimburse fairly for genetic tests; and physicians will need to increase their knowledge about genetics in general [6,101].

Liability serves as a wild card in the rollout of personalized medicine, though it is a factor that has received relatively scant attention to date [7–10]. As has been seen for many other scientific advances, liability can be a powerful driver for widespread behavioral change and the adoption of emerging technologies, an effect that may be beneficial or detrimental to the overall societal welfare depending on the circumstances. In the context of genetics, liability could drive the adoption of beneficial personalized medicine technologies that promote patient safety and allow patients to avoid unnecessary costs and side-effects. Alternatively, liability could force actors to prematurely deploy technologies that are unproven, wasteful and detrimental to healthcare. More likely, liability will have both effects in different scenarios and contexts.

To date, there have been but a smattering of lawsuits asserting liability claims based on personalized medicine. But the nature and dynamics of these types of personal injury and medical malpractice lawsuits is that the activity smolders at a low level for years until suddenly catching fire and engulfing entire companies, industries or practice areas in an inferno of expensive litigation. As new genetic technologies and procedures slowly infuse the practice of medicine, the potential impacts of liability relating to personalized medicine must be considered.

This article addresses the potential role of liability in personalized medicine, focusing primarily on physicians. The next section describes the dynamic nature of liability for medical technologies generally, noting the potential of innovative technologies and

future medicine part of fsg

procedures to trigger new liability pressures that can quickly catch fire if they gain momentum with some initial plaintiff victories. The next section then discusses the potential doctrinal dimensions of potential liability related to personalized medicine, concluding that physicians are likely to be at the greatest liability risk. After that, we summarize the existing case law on liability relating to personalized medicine, beginning with the handful of cases reported to date directly about personalized medicine, and then drawing lessons from the more mature litigation record for physician liability relating to prenatal genetic testing. Integrating the doctrinal and empirical findings from the previous sections, we next assess the potential physician liability in four specific scenarios involving currently available or proposed applications of personalized medicine. Finally, this article concludes by summarizing the liability dynamics and risks associated with personalized medicine and introduces some policy options that may help address the uncertainty currently giving rise to many of the liability risks.

Dynamics of litigation

Litigation is often a crapshoot. Clear-cut disputes rarely get decided in courtrooms. If the outcome of a dispute is predictable, the parties will usually come to some agreement rather than incurring the substantial transaction costs of litigating a case through discovery, pretrial motions and preparation, trial and appeal. In the US, plaintiffs' attorneys are generally the key decision-makers on whether or not a particular type of case is litigated because the contingency fee payment system allows them to collect payment only if their client's argument is successful. In personal injury cases, successful plaintiffs' lawyers can collect a windfall, often earning 30% or more of the plaintiff's judgment plus expenses under a typical contingency fee arrangement. If the plaintiff loses, however, the lawyer not only doesn't earn any revenue, but also loses the thousands or sometimes millions of US dollars he or she invested to bring the case to court, consisting of not only their own time, but the salaries paid to their junior attorneys and support staff fees to experts, discovery costs, court filing fees, and other expenses associated with litigation.

The consequence of this payment system is that plaintiffs' attorneys are often quite risk averse in bringing new types of cases when the evidence is relatively undeveloped and there is no track record to help them predict how such cases will fare in front of judges and juries. However, once a few cases have been successful on a particular issue, lawyers will respond to that favorable precedent, benefit from the evidentiary development in the previously litigated cases, and feel increasingly confident in their ability to secure their own favorable judgment. The more successes, the more plaintiffs and their attorneys will exhibit a herd response and converge on the new opportunity, creating a 'gold rush' mentality that can overwhelm and empty even the deepest-pockets of defendants. Examples abound, including the litigation surrounding Bendectin silicone breast implants, Vioxx®, fen-phen and the Dalkon Shield. Whether or not these products presented real risks, they were eventually removed from the market by a tidal wave of litigation, at the cost of millions or even billions of dollars.

Medical procedures and practices have also been the subject of asymmetrical litigation dynamics. Previous litigation experiences involving past innovations in medical technologies help predict how genetic technologies may be handled by the courts. Even when new technologies improve overall healthcare, they tend to increase liability as patients' expectations are raised and the gap in outcomes widens between early and slow adopters [11,12]. Thus, based on this historical pattern, the advent of a new set of medical technologies and procedures associated with personalized medicine would be likely to increase liability risks for physicians, both because of the increased patient expectations associated with the new innovations, and the inevitable gap in utilization between early and late adopters of these new technologies and procedures.

Historical analysis of medical malpractice litigation also reveals that increased litigation against physicians relating to a particular health outcome or procedure can significantly change physician practice. For example, after lawsuits started being filed against physicians who delivered children with cerebral palsy, the frequency of caesarean sections increased significantly [13]. Similarly, after a wave of lawsuits against physicians alleging missed nascent tumors on mammograms, the rate of breast biopsies following mammograms shot upward [14]. More generally, the fear of liability drives physicians to order more diagnostic tests and perform more procedures than medically indicated in order to protect against potential lawsuits, a practice known as defensive medicine [15].

Liability landscape for personalized medicine

Today, there is substantial uncertainty and disagreement about the appropriate use of genetics and other personalized medicine data in clinical care, giving rise to the types of disagreements and disputes that can spawn litigation [16]. On one hand, some experts claim certain personalized medicine techniques are ready for clinical application today, and several leading medical institutions have begun to deploy such techniques [4,17,18,102]. Experts with this perspective have expressed frustration that physicians and other stakeholders in the healthcare system have been too slow to uptake personalized medicine methods and tools [9,18]. Other experts, however, are more skeptical about the near-term deployment of personalized medicine, contending that such methods are not likely to benefit patient care and are not yet ready for widespread adoption [19,103]. We are thus currently at a critical and unsettled juncture in the implementation of personalized medicine, where much uncertainty and disagreement exists about which technologies and approaches are ready for use, what outcomes they will provide and who will pay for them. In such a period of uncertainty, the potential for liability is at its greatest [20].

These uncertainties can create liability risks for every entity across the personalized medicine lifecycle, including physicians, pharmacists, insurance companies, hospitals, laboratories and drug manufacturers. Of these potential targets, physicians are likely at the greatest risk for a variety of reasons [8]. For example, there is a well-established plaintiffs' bar experienced at suing physicians for medical malpractice. Physicians lack the types of defenses that at least partially protect other parties such as the learned intermediary doctrine, which allows drug manufacturers to shield themselves from failure to warn liability by simply listing risk information on their drug labels. The US FDA is increasingly requiring manufacturers to put pharmacogenomic data and warnings on patient package inserts for drugs, setting up physicians for potential liability if they fail to heed those data and warnings and an adverse event occurs [21]. In addition, only a handful of medical schools and training programs include formal genetics education, creating major disparities in the genetics proficiencies of practicing physicians that can be exploited by deft plaintiffs' lawyers. For these reasons, physicians are likely to have the greatest liability exposure with respect to the implementation of personalized medicine, and accordingly are the focus of this article.

To bring a successful medical malpractice case against a physician, a plaintiff must show that: the physician had a duty of care to the plaintiff; the physician breached that duty; the plaintiff incurred an injury; and the physician's breach caused the plaintiff's injury. Traditionally, the plaintiff was required to demonstrate the breach of a duty of care with expert testimony showing that the physician's actions were not in accord with the customary practice of physicians in the same specialty in that same local region. This traditional basis for establishing the standard of care is undergoing transition in many jurisdictions. First, the locality rule is being replaced in a number of jurisdictions with a national standard of care, in which a physician is not judged solely against similar practitioners in the same geographic region, but rather against doctors across the nation [22]. Second, the standard of care based on custom (i.e., what other doctors are doing) is giving way in many jurisdictions to a more objective 'reasonableness' standard in which the jury gets to determine whether a physician's actions were reasonable, regardless of the practice patterns of other physicians [23]. Under this new standard, a jury might find in some circumstances that the current practice of all or most physicians in a certain context was below the standard of care that could and should be achieved [24].

Finally, some jurisdictions are recognizing new causes of action that circumvent many of the defenses used by physicians under the traditional negligence-based medical malpractice cause of action. For example, an injured plaintiff may allege that the physician violated informed consent requirements by failing to ascertain or disclose relevant genetic information that could have influenced the patient's treatment options and choice. Each of these doctrinal developments are likely to increase physicians' liability risks relating to personalized medicine because they heighten or broaden the standard of care expected from a physician.

Other trends in addition to legal doctrine are increasing the liability exposure of physicians with respect to implementation of personalized medicine. The number of commercially available genetic tests continues to grow steadily, and now exceeds 2000 [104]. Physicians could potentially be hauled into court and found liable for failure to apply almost any one of the genetic tests in appropriate circumstances, yet most

physicians have not received significant training in genetics [105]. Another problem for physicians is that some genetic tests can cost upwards of US$3000, and in many cases are not reimbursed by the patients' health insurance policy [106]. The fact that a patient may not have the economic means to obtain a genetic test does not protect the physician from liability for failing to inform the patient of the test.

Existing case law

Unless providers reach a consensus about how and when to adopt personalized medicine technologies, court decisions involving those technologies are likely to play a lead role in setting the standard of care for their use within the medical field. While the medical community has been slow to adopt new genetic technologies, public expectations for personalized care have been fueled by fantastical accounts of futuristic medicine in best-selling novels, popular television shows, magazine covers and some news accounts of direct-to-consumer genetic testing services. Because juries in many jurisdictions now decide malpractice cases by considering how reasonable physicians should act rather than how most physicians act, public expectations play a major role in setting the standard of care and may influence jurors to hold physicians liable for failing to understand and use these highly publicized genetic technologies.

The handful of cases already decided by the courts involving clinical genetics, often involving prenatal testing, illustrate the liability threat that physicians face when dealing with this field. In addition to the traditional claims for negligence, genetic testing has also given life to ideas such as wrongful conception, wrongful birth and wrongful life, while creating new applications for claims such as loss of chance and duty to third parties. Although drug manufacturers, hospitals and pharmacists have all been the subject of these lawsuits, physicians may be the most vulnerable to claims by aggrieved patients and their families [8]. As the following litigated cases illustrate, physicians are vulnerable to a quickly-expanding array of lawsuits related to the screening, diagnosis, treatment and prevention of genetic conditions.

Failure to recognize genetic risk

Despite the current lack of formal genetics training in medical education, courts have held physicians responsible for being able to recognize patients at high risk for a variety of genetic conditions. In 1981, a federal court found a doctor negligent for failing to screen a woman's fetus for Down syndrome based on the fact that her sister had the condition. Though only 2% of Down syndrome is inherited and the screening technology for Down syndrome was still being developed at the time, the court in this case found that the woman's family history should have prompted the physician to perform more rigorous screening, and thus awarded the mother $1.5 million [25,26]. More recently, a court found a physician negligent after his patient's child was born with the same rare genetic condition he had failed to diagnose in the child's sibling. Although the physician had only seen the condition a few times in his career and it had not yet fully manifested in the sibling, the court awarded the family $23.5 million for the physician's failure to recognize the disease [27]. Similarly, a New Jersey (NJ, USA) court awarded $14 million to a family after the physician failed to recognize that the mother's ethnicity put their child at high genetic risk for a rare blood disorder [28].

Of course, most such cases settle, for which information is generally not available, and other cases are decided in favor of the physician, and tend not to be appealed, making a published decision (which are often at the appellate level) less likely. Notwithstanding these uncertainties, the willingness of at least some courts to hold providers responsible for staying informed about newly emerging technologies, rare disorders and a broad set of risk genetic factors suggests few limits on the scope of liability for physicians in this field.

A Texas (TX, USA) court recently outlined what seems to be a growing consensus about what is expected from doctors in handling patients with genetic conditions. The expert testifying to the standard of care in this case recognized both the duty to identify patients' genetic concerns and to refer them to appropriate resources when appropriate: "An obstetrician confronted with this information has the option of either knowing the information and doing the counseling themselves, or referring the patient to a subspecialist in medical genetics or maternal fetal medicine" [29]. Similar expectations have been imposed by courts related to a wide variety of genetic diseases, including relatively common conditions, such as sickle cell anemia and Fragile X syndrome, but also much rarer disorders to which most physicians have little, if any, exposure (e.g., Smith-Lemli-Opitz syndrome and anhidrotic ectodermal dysplasia) [27,30–32].

Loss of chance

The loss of chance doctrine poses one of the greatest threats to physicians, whose limited knowledge of genetics may reduce the chances of favorable outcomes for their patients in a variety of ways. Traditionally, this claim required significant reductions in the patients' probability for a positive outcome, so its application has been fairly limited. However, many courts are now allowing claims to go forward even when the physicians' negligence increases the risk of harm only slightly. Related to genetics, physicians who fail to identify or explain genetic risk factors may be liable to patients who lose the chance to prevent or mitigate an injury because of the physician's negligence.

Delays in the identification and treatment of genetic diseases both fit within the loss of chance framework. A New York (NY, USA) court recently found a physician negligent for taking 3 weeks to diagnose a child with propionic acidemia, an enzyme deficiency affecting just 1 in 150,000 births [33]. By the time the child was diagnosed, he had suffered irreversible brain damage that could have been prevented with a more prompt diagnosis, and the court awarded the family $3.5 million in damages [34]. Although this case did not formally invoke the loss of chance doctrine, it may serve as a harbinger of claims to come. Its result implies an expectation that physicians should be well versed in quickly recognizing a growing number of genetic disorders, or at least recognizing the possibility of a genetic disease and making the appropriate referral.

Informed consent

Physicians have also been held liable in their handling of genetics by failing to fully obtain informed consent related to diagnostic and treatment procedures. Informed consent claims are increasingly powerful tools for patients, especially as courts transition towards a patient-centered approach to this doctrine, which requires physicians to disclose all information that reasonable patients would consider material to their decision-making (rather than the information that reasonable physicians would consider material, as the traditional doctrine required). This cause of action is similar to loss of chance in that plaintiffs must claim that they would have made different decisions and potentially averted their injuries if they were provided the right information. In 2008, for example, a federal court held a physician liable when his patient gave birth to a child with Down syndrome. The woman had turned down the chance to test for the condition at 15 weeks gestation, but claimed she would have undergone a different form of testing offered at 11 weeks if the doctor had told her about that type of testing. The court awarded her $2.5 million based on her claim that if she would have been told about the earlier screening option, she would have aborted the fetus [35]. In general, this doctrine allows any patients who suffers injuries that could have been avoided by making different decisions about their own care based on genetic information or tests not disclosed by their physician to hold that physicians liable for any resulting injuries, placing great weight on physicians' knowledge of available genetic tests.

Failure to warn

Traditionally, physicians have no responsibility to anybody except patients with whom they've entered into a professional doctor–patient relationship. However, exceptions have been carved out of this rule in extreme circumstances. The Tarasoff court made headlines in the 1970s for holding a psychiatrist liable for failing to warn a woman with whom he had no prior contact that his patient may pose a threat to her [36]. This case represented a major expansion of a psychiatrist's duties at the time, and has been applied only sparingly since then. Recently, however, some courts have drawn an analogy between the psychiatrist's duty to warn about his murderous patient to contemporary physicians' duty to warn family members of their patient about the patients' potentially risky genes, significantly expanding physicians' responsibilities in the process.

At least two courts have held physicians responsible for failing to tell patients' relatives that they may share a risk-conferring mutation with the patient, even in situations in which neither the physician nor the patient has a relationship with those relatives [31,37]. One court held that a physician could be negligent for failing to tell his patient's daughter about her father's diagnosis of hereditary colon cancer, though she was only 10 years old at the time of his death, and the father intentionally hid the diagnosis from his family. That court found the duty to protect at-risk individuals outweighed the duty to maintain patient–doctor confidentiality: "We see no impediment, legal or otherwise, to recognizing a physician's duty to warn those known to be at risk of avoidable harm from a genetically transmissible condition. In terms of foreseeability especially, there is no essential

difference between the type of genetic threat at issue here and the menace of infection, contagion or a threat of physical harm" [38]. Opinions like this are complicated by the conflicting yet traditional notion that a doctor's duty stops with warning the patient to tell family members. Medical privacy laws at the federal (e.g., Health Insurance Portability and Accountability Act) and state levels further complicate the physician's obligations in such situations. These confusing and inconsistent instructions thus create a situation in which there is no safe decision for a physician to make when disclosing sensitive genetic information.

Four examples

This section provides four hypothetical examples where a physician may be held liable for medical malpractice relating to personalized medicine. In setting forth these scenarios, we do not intend to suggest that physicians should or necessarily would be held liable for their actions, only that they might be held liable. Given the volatile mix of disagreement within the published literature and among credentialed experts, the idiosyncrasies of individual juries, juries, experts and attorneys, and the importance of intangible influences on litigation outcome such as the group dynamics of a particular jury or how well a particular lawyer performed on a specific day, the four scenarios described below, which involve different types and uses of genetics tests, could lead a jury to find a physician liable for medical malpractice in at least some instances.

Example 1: *BRCA* testing

This first example involves a physician's duty to warn patients about inherited disease predisposition genes. Among the strongest and best validated of these disease predisposition genes are the *BRCA1/2* genes for breast cancer, as women carrying a mutation in either of these genes have a 50–85% risk of breast or ovarian cancer [39]. Interventions such as prophylactic bilateral radical mastectomies and oophorectomies have been shown to substantially reduce the risk of cancer in asymptomatic women carrying a *BRCA1/2* mutation [39]. Various expert evidentiary reviews have recommended genetic testing of women who have certain risk factors for carrying one of these mutations, such as having two first-degree female relatives who have developed breast cancer. These expert guidelines are not binding on courts, and so it is possible that a judge or jury could hold a doctor responsible for failing to recommend genetic testing for a woman who does not meet the screening recommendations in the guidelines. For example, many of the guidelines may not be relevant for a woman with few if any available first degree female relatives, such as an adopted woman with unknown birth parents, or a single child family in which the mother is no longer available. In such cases, the lawyer for a woman who develops breast cancer may argue that the physician should have recommended *BRCA1/2* testing even if the evidence of risk is less than called for in the guidelines to recommend testing.

A physician could potentially be sued if he or she sees an asymptomatic patient with a strong family history of breast cancer, but does not recommend the patient undergo genetic counseling or testing. If that patient subsequently develops breast cancer, she or her surviving family members could bring a lawsuit alleging that the physician breached a duty to warn her of her potential genetic risk, and the failure to recommend genetic testing resulted in the patient's 'loss of chance' to have prevented or successfully treated the disease. The plaintiff would argue that if her doctor had warned her about her genetic risk, she would have undertaken testing for *BRCA1/2*, and if she had tested positive, would have either undergone prophylactic surgery to prevent the disease or performed more frequent surveillance to detect the disease in an earlier, more treatable stage. At least one doctor has already been sued by a patient for failing to recommend counseling or testing for the *BRCA1/2* mutation, leading the patient to undergo an unnecessary mastectomy [40]. The jury in this case found that the treating physician had adequately recommended genetic counseling, but that the patient declined to seek such counseling because she could not afford the *BRCA1/2* genetic test.

Example 2: gene-expression profiling

A second type of genetic test that could potentially lead to liability is gene-expression profiling. This test measures changes in gene expression, rather than inherited genetic changes, to classify a diseased tissue (such as a tumor) with respect to its prognosis and best treatment options. Many types of tumors can now be classified based on different patterns of gene expression into subcategories that previously were indistinguishable using traditional clinical parameters. These different subcategories of tumors often have a very different prognosis, including risk of recurrence, which may affect treatment or management regimens. The first commercial

tests are now available to identify such patterns. For example, the Onco*type* DX® assay is marketed by Genomic Health, Inc. (CA, USA), and screens the expression of 21 genes to predict the risk of cancer recurrence for certain subtypes of breast cancer. Expert opinion is currently divided on whether physicians should recommend gene-expression profiling of tumors in some or all patients, and this difference of opinion and uncertainty is likely to increase as more tests become available [41–43]. The Evaluation of Genomic Applications in Practice and Prevention Working Group, an expert panel established by the Centers for Disease Control and Prevention (CDC) to make recommendations on the clinical use of genetic tests, concluded in 2008 based on a comprehensive evidence report it commissioned that there was "insufficient evidence to make a recommendation for or against the use of tumor gene-expression profiles to improve outcomes in defined populations of women with breast cancer" [44]. Accordingly, "until more data are available, clinicians must decide on a case-by-case basis if the use of a gene-expression profile test adds value beyond the use of the current prognostic markers" [44]. This uncertainty opens the door to disparate physician practice and potential liability.

The uncertainty surrounding gene-expression profiling leads physicians to face a 'damned if they do, damned if they don't' dilemma. If the physician recommends a gene-expression assay, and the test results suggest that the patient has a low risk of recurrence and they decide not to undergo chemotherapy as a result, the physician might face liability risks if a tumor recurs. The plaintiff's lawyer could likely find an expert who would testify that the gene-expression assay was not sufficiently validated for such decisions, and thus the physician acted negligently by recommending the test or for not trying to dissuade the patient from foregoing chemotherapy based on the (allegedly) unreliable test results. Conversely, in an appropriate case, the same physician could be sued for being too conservative and not recommending the gene-expression test to another patient. In this hypothetical situation, the patient may be classified as having a low risk of recurrence using traditional clinical parameters, and therefore elects not to undertake chemotherapy, and is then disappointed to find the cancer reoccurs nonetheless. In this case, the patient's lawyer may find an expert to testify that the gene-expression assay is the most reliable predictor of recurrence, and if the doctor had recommended such a test, it would have given a more accurate risk of recurrence than the traditional clinical parameters. To buttress this claim, the plaintiff would likely need to undertake the test after the fact to show that it does indeed indicate a higher risk than suggested by the traditional clinical parameters.

Example 3: drug–gene interaction (pharmacogenetics)

The third class of genetic tess that may create a liability scenario involves the growing number of genetic variants that affect patients' responses to drugs – in some cases resulting in the drug being ineffective, and in others causing a potentially adverse side effect. Given that drug side effects kill over 100,000 Americans each year, and genetic variants likely contribute to a considerable proportion of those fatalities, there is a potentially large pool of prospective plaintiffs who could bring lawsuits alleging that a physician's failure to recommend genetic testing for relevant variants before prescribing a drug contributed to a patient's death or adverse effect [45]. As in the previous example, the applicable standard of care – in this case whether and which gene variants should be tested for prior to prescribing a drug – is likely to be highly indeterminate and contested. Consider clopidogrel (Plavix®), the second most prescribed drug in the world, which is taken by more than 2 million patients every year to prevent the formation of a stent-induced blood clot, a frequent and often fatal occurrence among patients following heart surgery [46]. It has been well established that individuals vary significantly in their response to clopidogrel, and variations in two genes (*CYP2C19* and *PON1*) contribute significantly to the wide variation in drug response, although the studies reported to date are not entirely consistent in the role they attribute to this genetic variation [47–50]. When clopidogrel is prescribed, an estimated 1–2% of patients still suffer serious adverse events, presumably because, in most cases, the clopidogrel failed to prevent clot formation as expected [51]. The widespread use of this drug, combined with the relatively high rate of side effects and the well-characterized genetic influence on efficacy, generates thousands of potential plaintiffs each year.

Given this unsettled situation, some experts recommend that genetic testing should now be a part of routine clinical practice when prescribing clopidogrel, while others disagree [52]. The FDA further complicates the appropriate standard of care by requiring a black box warning about the genetic risks associated with

clopidogrel while paradoxically not requiring physicians to conduct genetic tests before prescribing the drug. Another complication for both the prescribing physician and the legal fact-finder determining causation and liability is that interindividual differences in susceptibility to adverse side effects from drugs is affected by many other factors in addition to genetics, including age, gender, hepatic and renal status, nutrition, smoking and alcohol intake, and drug–drug interactions. Thus, while a patient with a relevant genetic variant (which would probably need to be demonstrated by after-the-fact genetic testing) who is not referred for a genetic test and reacts adversely to clopidogrel may have a viable lawsuit against the prescribing physician, the outcome will be dependent largely on the specific facts of that case and the skills and performance of the particular attorneys, experts and jury members involved in that case.

Example 4: whole-genome sequencing

The final example involves a very recent type of genetic testing that is only in early research stages at this time but could become part of clinical care relatively quickly in at least some practices. The potential for rapid adoption of whole-genome sequencing may fuel a discrepancy in care that could leave slower adopter physicians and provider institutions at risk of liability. This technique is already being used, for example, to sequence the entire genome of a cancer patient's tumor and compare it to that same patient's inherited genome [53,54]. Genetic changes revealed in tumors using this comparative approach could be used to identify otherwise unexpected treatment regimens that target the particular molecular identity of the tumor. Although this method has only been used in research studies on a relatively small number of patients to date, the results today are promising and have generated significant interest in the method. While the technique is too expensive and experimental to be used in routine cancer care now, leading institutions and physicians may adopt the technology on selected patients in the relatively near future. As will be the case for any new, expensive and highly technical new medical procedure, a gap is likely to quickly grow between those providers at the leading edge of technology and care, and those that lack the resources, expertise and wherewithal to keep up with the leaders in the field or those physicians who are more cautious about adopting new technologies until they have a proven track record. Especially as more and more jurisdictions migrate to a national rather than local standard of care, this growing discrepancy between the leaders and the slow adopters creates an opening for litigation and liability [22].

Slow adopters of whole-genome sequencing and related genetic technologies may face liability risk in a number of different scenarios. For example, tissue from the tumor of a patient who succumbed to cancer at a local hospital may be sent to a leading laboratory conducting a cancer genetics research project, where it might be discovered that the tumor had a specific mutation that had been successfully targeted by therapies given to cancer patients at a different hospital, where their tumors had been analyzed using whole-genome sequencing. In this situation, the family of the deceased patient may be able to bring a lawsuit alleging that the treating physician and hospital had failed to apply the appropriate standard of care in not conducting whole-genome sequencing of their family member. Once again, the outcome of such a case would likely depend on very context-specific facts of the particular case and the participants in the trial, which would be hard to predict at the outset.

Conclusion

Based on the historical patterns of increased liability risks following medical technology innovation, as well as the stringent and unpredictable expectations that judges and juries have placed on physicians in genetics-related litigation to date, physicians are increasingly vulnerable to liability as the approaching wave of personalized medicine begins to envelop clinical practice. The wide discrepancies between physicians in their willingness to adopt personalized medicine technologies, the rapid pace at which new data and technologies are becoming available, the large number of patients dying every year from drug side-effects that likely have some genetic attribution, and the doctrinal shifts in medical malpractice liability including the demise of the locality rule and the increased prominence of the reasonableness standard, all contribute to the potential for impending liability risk for physicians. The absence of many lawsuits today should not provide much comfort, given that the typical dynamics of litigation are that it starts slow, but then picks up momentum in a cascade that is very hard to stop once it starts.

What can be done to head off this potential liability explosion? It is in the interest of both physicians and patients to ensure that personalized medicine approaches are applied in a careful and appropriate manner to prevent adverse effects and to improve clinical outcomes when the new technologies offer such benefits. At the same time, premature or unsupported use of such technologies, perhaps driven by defensive medicine in response to liability pressures, can jeopardize the most effective care for patients and unnecessarily increase medical costs.

One factor that can help reduce liability risks is to improve the knowledge and training of physicians on genetics-based healthcare. Relatively few doctors receive significant training during medical school in genetics and related molecular sciences, and thus lack the background needed to effectively integrate new genetic findings into their practice. The availability of more authoritative evidence-based guidelines on when genetic testing is and is not warranted could provide physicians with a more rational approach to genetics in the short term. Without credible guidelines to guide their decision-making, physicians are currently forced to wade on their own through a stack of conflicting studies, expert advice and recommendations on whether or not genetic testing is indicated and useful in particular circumstances and patients. Guidelines have had a checkered history, with many problems such as conflicts of interest, out-dated recommendations and noncompliance, yet standardized guidelines have often enhanced the quality and efficiency of clinical care [55]. Unfortunately, one source of credible guidelines, the Evaluation of Genomic Applications in Practice and Prevention Working Group on which one of us served (Doug E Campos-Outcalt), was recently disbanded due to funding shortages, portending an even more pronounced absence of clear, authoritative guidance that physicians can follow in the future. Given this development, there is a need for professional societies, governmental organizations such as the US Preventive Services Task Force and the CDC, or payers and health plans to step up to the plate and provide greater certainty for physicians by providing genetic testing recommendations. Other possibilities that may help physicians include liability reform, strengthening of the Clinical Laboratory Improvement Act of 1998 to improve genetic testing by laboratories, limits on those direct-to-consumer genetic tests that are misleading or deceptive, and the creation of a genetic test registry by the NIH [56]. In the absence of such actions, physicians are stranded out in the wilderness of genetic indeterminacy, with the wolves howling on the horizon. Now is the time to address this problem before it becomes too late.

Future perspective

Approximately 100,000 people die every year in the USA from drug side effects [45]. Medical innovation transforms what has been thought of as 'natural risk' into 'medical risk' that can and should be prevented, and ultimately 'liability risk' for which the patient seeks compensation through the courts [57]. As a result of this dynamic, it is quite possible that 10 years from now, physicians may be beset by perhaps the biggest surge in liability risk (and associated malpractice premiums) ever. Just as other clinical technologies have sparked increased malpractice liability because of disparities in practice, unfamiliarity with the new technologies, and increased expectations by patients, the fundamental transformation of medicine promised by personalized medicine could carry with it an equally fundamental shift in liability exposure for physicians. One leading medical expert recently opined that "the discrepancy between current medical practice and the capabilities for improvement is greater now than at any time since the early part of the 20th Century" [58]. The current gap between current practice and that which will soon be enabled by new personalized medicine technologies could arguably mean the difference between life and death for thousands of patients per year. Physicians are likely to be hauled into court and called to account for this discrepancy unless steps are taken to provide physicians with better education and guidelines to integrate the new data and technologies into their clinical practice. The window of opportunity to act is short. Once the litigation snowball starts to roll, it will quickly become unstoppable.

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Executive summary

Background

- The adoption of personalized medicine has been slowed down by a number of factors such as regulatory and approval barriers, low reimbursement for genetic technologies, and low awareness of genetic advances among providers.
- Due to these factors, clinical adoption of personalized medicine technologies has fallen behind public expectations, creating a gap that breeds liability.

Dynamics of litigation

- Litigation on a particular issue often starts slow but can quickly snowball after just a few cases are tried successfully and plaintiffs' lawyers see that success in a particular practice area is possible.

Liability landscape for personalized medicine

- The uncertainty surrounding the appropriate use of personalized medicine technologies creates a huge risk of liability because it is possible to find evidence and experts to contradict almost any decision physicians make related to genetic technologies.
- Among potential targets of lawsuits, physicians may be the most vulnerable to future lawsuits.

Existing case law

- Physicians have already been held liable for their negligence in the use of genetic tests, most notably by extending the traditional doctrines of informed consent, duty to warn and loss of chance.

Examples of potential lawsuits

- Because of differences in physician education and hospital testing capabilities, new technologies are likely to be rapidly adopted by some providers and not adopted by others.
- *BRCA* gene testing, gene-expression profiling of tumors, drug–gene interaction screening and whole-genome sequencing are all technologies that have entered or are likely to enter clinical practice soon, are likely to be adopted disparately by providers, and will therefore generate substantial liability risk for physicians.

Conclusion

- Personalized medicine technologies are likely to give rise to new and substantial liability risks.
- Among the groups involved in the lifecycle of personalized medicine technologies, physicians may be the most vulnerable to liability.
- The medical community needs to make a concerted effort to resolve the uncertainties and disparities surrounding personalized medicine in order to avoid a future in which litigation, rather than sound science and policy, directs the practice of personalized medicine.

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Biotech Briefing Fall 2011

Message From the Biotechnology Law Committee Co-Chair

Welcome to the Fall 2011 issue of *Biotech Briefing*. This issue of the *Biotech Briefing* comes to you after a hiatus in publication, and we are glad to be back. This issue contains two articles on timely topics: whole genome sequencing, and *Stanford v. Roche*. The article on whole genome sequencing was authored by Gary Marchant (Professor of Law at the Sandra Day O'Connor College of Law, Arizona State University) and Rachel Lindor (Research Fellow at the Sandra Day O'Connor College of Law and Mayo Medical School). Sean O'Connor (Professor of Law at the University of Washington) authored the second article on the Supreme Court's recent decision in *Stanford v. Roche*. We thank our authors for their contributions. Please let me know (kcarver@cov.com) if you are interested in contributing to our Winter issue.

☐ Krista Carver
Covington & Burling LLP

The Game Changer: Whole Genome Sequencing

Gary E. Marchant[1] and Rachel A. Lindor[2]

One decade ago the first draft of the human genome sequence was published with great expectations for rapid, unprecedented medical breakthroughs. In fact, DNA sequence data have enabled steady and impressive progress in understanding and treating human disease.[3] Yet, critics argue that practical benefits have been slower and fewer than anticipated, and that hopes are diminishing for identifying blockbuster genes at the root of serious diseases in large numbers of people.[4]

The genomic revolution is about to receive a major kick-start, though, with the advent of whole genome sequencing (WGS), a process that reveals the DNA sequence of an individual's entire genome. Over the past few years, WGS has moved quickly from a future scenario to a current research reality and is now moving into the clinical realm, raising many profound medical, legal, ethical, and social issues. This article provides a brief overview of these issues, after first describing the current status and applications of WGS. The bottom line is that WGS is about to become a major game changer not only for science and health care, but also in more profound and long-ranging ways.

Status of WGS

In 2004, the federal government set a target of $1000 for sequencing an entire human genome, at which point it would be economically feasible to integrate WGS into clinical care. That goal is now within reach. The traditional Sanger method of sequencing DNA base-by-base has been superseded by "next-generation" and soon "third generation" sequencing technologies that are capable of massive parallel sequencing at exponentially reduced cost and time. Several companies are now commercializing these technologies, competing to be the leader in this emerging new industry. This technology push has driven down the cost of sequencing exponentially, from the $100 million required to sequence the first genome to the commercial availability today of WGS for $10,000.[5] The cost of WGS is expected to hit the $1000 goal within

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[3] Eric S. Lander, *Initial Impact of the Sequencing of the Human Genome*, 470 NATURE 187 (2011).

[4] Nicholas Wade, *A Decade Later, Genetic Map Yields Few New Cures*, N.Y. TIMES, June 12, 2010.

[5] *E.g.*, Illumina, http://www.everygenome.com.

1-4 years, with many expecting the cost to drop as low as $100 in the years to follow.[1]

WGS likely will have enormous practical implications for both health care and the law. The rapidly falling cost of sequencing is making it increasingly affordable for individuals to have their genomes sequenced. In 2009, for example, fewer than 100 genomes had ever been sequenced, but over 2000 were sequenced in 2010 and an estimated 25,000 will be sequenced this year.[2]

Applications

The dramatically reduced cost and time required for WGS has opened the door to clinical applications. Recent findings suggest we all carry 100 or more rare genetic variants that could significantly increase our risk of specific diseases, most of which would not be detected by existing genetic screens that are limited to more common genetic variants. [3] There are already several noted examples in which an individual with an intractable disease underwent WGS and revealed a rare genetic variant that facilitated life-saving treatment.[4] As the cost of WGS continues to drop, the potential health and preventive benefits of identifying the rare genetic variants we all carry will likely spur greater use of sequencing by individuals, health insurers and providers.

WGS has been especially fruitful in efforts to personalize cancer treatment. Several leading cancer institutes have begun to sequence the entire genomes of tumor cells in order to compare them to patients' healthy cells. This comparative analysis reveals critical genetic changes in the cancer cell that have allowed providers to tailor treatment options to individual patients.[5]

The falling cost of sequencing technology will eventually make sequencing a more efficient method of patient care than traditional genetic testing, which relies on a different test for each disease. For example, personalized medicine is moving health care in the direction of testing for polymorphisms in drug-metabolizing genes prior to prescribing a growing list of drugs. Since the individual gene tests can range in price from several hundred to several thousand dollars, a once-in-a-lifetime WGS for $1000 or less will drive health insurers and payers to adopt WGS in the near future.

Further into the future (but perhaps within the next decade), WGS will be used for an ever-growing and often more controversial set of applications. Many experts predict that all citizens will eventually have their entire genomes sequenced. Researchers will use the sequences of volunteers to look for all sorts of correlations with various traits, including behavioral tendencies and performance outcomes. Parents might start using WGS to select their offspring using preimplantation genetic diagnosis (PGD). Police may seek access to stored genome sequences to assist forensic investigations. Indeed, as the power of ubiquitous gene sequencing becomes apparent, the potential applications are almost limitless.

Legal, Ethical and Social Issues

WGS raises numerous legal, ethical and social issues, both now and in the future, which are briefly summarized below:

Patenting: Over 4000 human genes are currently patented, raising the issue of whether sequencing every gene of an individual infringes those patents and requires thousands of licenses. [6] Although the issue has not yet been resolved, there is a credible argument that sequencing a

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[1] Andrew Pollack, *The Race to Read Genomes on a Shoestring, Relatively Speaking*, N.Y. TIMES, Feb. 9, 2008.

[2] Radoje Drmanac, *The Advent of Personal Genome Sequencing*, 13 GENET. MED. 188 (2011).

[3] Kelly E. Ormond et al., *Challenges in the Clinical Application of Whole-Genome Sequencing*, 375 LANCET 1749 (2010).

[4] *E.g.*, E.A. Worthey et al., *Making a Definitive Diagnosis: Successful Clinical Application of Whole Exome Sequencing in a Child with Intractable Inflammatory Bowel Disease*, 13 GENET MED 255 (2011).

[5] Boris Pasche & Devin Absher, *Whole-Genome Sequencing: A Step Closer to Personalized Medicine*, 305 JAMA 1596 (2011).

[6] The patentability of human genes is currently being litigated in the context of Myriad's BRCA patents. *See* Ass'n for Molecular Pathology v. PTO, 669 F.Supp.2d 365 (SDNY 2009) (rejecting patents for human genes), *rev'd*, __ F.3d __, 2011 WL 3211513 (C.A.Fed.), 99 U.S.P.Q.2d 1398.

gene and then comparing the sequence to published sequence data to identify the variant an individual carries does not infringe the patent, unlike traditional gene testing that often requires use of a patented gene segment as a probe.

Informed Consent: Traditional informed consent processes, aimed at ensuring research participants understand all of the risks of their participation, are likely not feasible for WGS. Because of the complexity of genetic information and the potential scope of findings, recent estimates suggest that consenting patients to WGS using traditional methods would take 6 hours.[1] The potential ramifications of genetic testing for family members and the likelihood that sequenced genomes will be used for future research also complicate traditional paradigms for consent.

Disclosure of Incidental Findings: The sheer amount of data captured by WGS will drastically increase the frequency of incidental findings—those unrelated to the original purpose of the test but with potential clinical or other significance for patients. There is much debate about if, when, and how these findings should be disclosed to patients. Some argue there is a moral duty to inform individuals of any significant or treatable finding, as is expected for most other clinical testing. Others argue that the 3-4 million variants expected per person and the constantly changing understanding of their significance would make this expectation impossible to meet.[2] Indeed, one estimate suggests that delivering WGS findings under the current paradigm would require five hours.[3]

Confidentiality/Privacy/Storage: As more and more people have their genome sequenced, where will that valuable but sensitive data be stored? Will it be given to the patient, and if so, in what format and with what annotation? Currently, some companies provide genomic data over the internet, but others concerned about online security provide the information only on a hard disk. Will the data be accessible to the patient's medical providers, possibly linked to his or her electronic health record? Will police or private litigants be able to gain access to that data using a warrant or subpoena?

Clinical Laboratories Improvement Amendments (CLIA): Most WGS is currently being done in a research setting, often in non-CLIA certified laboratories that, under CLIA, are not permitted to report back health data to subjects. A problem arises if a researcher identifies a gene variant in a subject's DNA sequence that presents a significant health risk that the subject could take action to mitigate. Would the laboratory be required to retest the sample in a CLIA lab before reporting back the result? Who would pay for this additional cost?

FDA Regulation: An FDA advisory committee recently recommended that the FDA restrict direct-to-consumer genetic testing to tests ordered by a physician. If the FDA adopts this advice, will it also try to restrict consumers from obtaining their own complete genomic sequence?

Liability: The availability of WGS is likely to open many new liability fronts. Physicians may be at risk for failing to warn a patient of a known risk factor present in their genome or for prescribing a drug that the patient's DNA sequence indicates is potentially hazardous or ineffective. In product liability and toxic tort cases, defendants will seek an injured plaintiffs' genome sequence for clues of susceptibilities to alternative causes that may have caused the injury, while plaintiffs will try to use their enhanced genetic susceptibility or induced mutations to prove causation or duty.

Social-Ethical: WGS will reveal enormous information about our individual predispositions and predilections, going well beyond health data to include traits relating to our aptitudes, capabilities, and tendencies. The potential applications of these data are almost unlimited but will have profound implications for education, career planning, sports, criminal culpability, mate selection, and many other areas.

Conclusion

WGS will be a game changer, for our health care in the near term, and much more broadly for our personal well-being and social lives in the longer term. At each step in its rapid

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[1] Jonathan S. Berg et al., *Deploying Whole Genome Sequencing in Clinical Practice and Public Health: Meeting the Challenge One Bin at a Time,* 13 GENET. MED. 499 (2011).

[2] *Id.*

[3] *Id.*

development, WGS will likely raise a myriad of legal, ethical and social issues, for which we have provided but a cursory introduction here.

Practical Implications of *Stanford v. Roche* for Ownership of University Inventions

Sean M. O'Connor, J.D., M.A.[1]

The discovery and commercialization of biotechnology innovations often rely on collaborations between universities and for-profit firms. The federal government funds much of university life sciences research and, under the Bayh-Dole Act,[2] has some rights to research arising from that funding. Two important strands of invention ownership issues in this web of collaboration arose under litigation that culminated in the recent Supreme Court decision *Board of Trustees of Leland Stanford Junior University v. Roche Molecular Systems, Inc.* ("*Stanford v. Roche*").[3] The first is the question of whether Bayh-Dole trumps any other invention assignment agreements when federal funding was used in any part for the invention. The second is whether a 1991 development in Federal Circuit case law regarding invention assignments is binding federal common law. While the Supreme Court limited itself to the first question—because the petition for certiorari was so limited—some of the justices addressed the second in a concurrence and a dissent. Accordingly, this article focuses on practical implications of the Supreme Court's holding, including the issues it left open.

The salient facts of the case are as follows. Dr. Mark Holodniy became a research fellow at Stanford University in 1988.[4] He executed Stanford's then standard Copyright and Patent Agreement (CPA) which provided that he "'agree[d] to assign' to Stanford his 'right, title, and interest in' inventions resulting from his employment" at Stanford.[5] His work required him to learn and use the polymerase chain reaction technique (PCR) that Cetus Corporation had pioneered. Cetus was already collaborating with Stanford on research in this area, and Holodniy's supervisor arranged for him to learn PCR at Cetus and pursue a substantial part of his research there with Cetus employees. Upon arriving at Cetus, Holodniy executed Cetus' Visitor's Confidentiality Agreement (VCA), which provided that he "'will assign and do[es] hereby assign' to Cetus his 'right, title and interest in each of the ideas, inventions and improvements' made 'as a consequence of [his] access' to Cetus."[6] After nine months, during which the invention at the heart of this case was conceived, Holodniy returned to Stanford to test and refine the invention. He worked with colleagues there, allegedly under federal funding.[7] In 1991, Roche Molecular Systems, Inc. (Roche), purchased all of Cetus' PCR-related assets. Over the next few years it conducted clinical trials on the PCR HIV technique as it had been developed while Holodniy was still at Cetus, and then developed and distributed commercial kits worldwide.[8] In 1992, Holodniy and his Stanford colleagues finished testing and refining the invention. Stanford then obtained invention assignments from them all and filed patent applications on the technique.[9] Three patents ultimately issued, in 1999, 2003, and 2006.[10] In 2000, Stanford approached Roche about taking a license to the Holodniy patents, but Roche responded that it was a co-owner or licensee of the inventions—under the terms of the VCA, some materials transfer agreements, and under common law shop rights—and declined to take a license.[11] Stanford sued Roche for patent infringement in 2005.[12]

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[2] P.L. 96-517 § 6 (Dec. 12, 1980).

[3] 131 S. Ct. 2188 (2011).

[4] *Id.* at 2192; Trustees of Leland Stanford Junior University v. Roche Molecular Systems, Inc., 583 F.3d 832, 837 (Fed. Cir. 2009).

[5] 131 S. Ct. at 2192.

[6] *Id.*

[7] 583 F.3d at 838; 131 S. Ct. at 2192. Stanford was never able to produce the government funding agreement.

[8] 131 S. Ct. at 2192.

[9] 583 F.3d at 838; 131 S. Ct. at 2192.

[10] *Ibid.*

[11] 583 F.3d at 838.

[12] 131 S. Ct. at 2193.

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