Genetic Variation in Clotting Response as a Source of Physician Liability: Can Predictive Genomics Curb Negligence Claims?

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Introduction

Acute myocardial infarction ("MI") has historically been,² and continues to be, the main cause of mortality in the United States.³ Close to one million Americans are impacted annually in spite of a better awareness of the presenting symptoms, and another one quarter of a million people die prior to presentation at a hospital. However, the survival rate for those patients who are hospitalized with MI is approximately ninety-five percent, representing a significant improvement in survival.⁴ The decreased mortality rate is directly related to improvements in emergency medical response and

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treatment methods, especially pharmacological intervention.\textsuperscript{5}

Most MI's are caused by a disruption in the vasculature, the layer of smooth, thin cells which line the heart's blood vessels and cavities, secondary to a build-up of atherosclerotic plaque.\textsuperscript{6} This plaque, which is unstable, stimulates the formation of a clot, thereby obstructing the flow of blood in the artery.\textsuperscript{7} If the resultant occlusion persists long enough, cellular necrosis sets in and is irreversible.\textsuperscript{8} Having developed over a period of years, the atherosclerotic plaque may suffer erosion, eventually leading to a forcible separation of the smooth cells lining the vessel.\textsuperscript{9} Any degree of disruption of this endothelial layer of smooth, thin cells can cause the formation of a clot, or thrombus, through a platelet-mediated activation of the enzymatic coagulation cascade.\textsuperscript{10} The final physiologic process is thrombosis.\textsuperscript{11} MI can result if a thrombus is large enough to completely occlude coronary blood flow for a sufficient time period.\textsuperscript{12}

Pharmacologic intervention has been aimed at the platelet-mediated coagulation cascade. Anticoagulation treatments have proven tremendously important in the prevention and treatment of acute clotting incidents, including stroke, and deep venous thrombosis.\textsuperscript{13} Heparin has been a key player in the prevention and treatment of thrombosis.\textsuperscript{14} Rigorous clinical trials have established that low molecular weight heparins are powerful and safe anticoagulant options for patients with MI, as well as for those with deep vein thrombosis, pulmonary embolism, and unstable angina.\textsuperscript{15} In addition, heparin can play a major role in preventing thromboembolic events in patients who suffer cerebrovascular accidents.\textsuperscript{16}

Nevertheless, anticoagulation therapy can manifest as an adverse clinical outcome, usually as a result of a hemorrhagic event or inappropriate platelet

\textsuperscript{5} See Ryan et al., supra note 4.
\textsuperscript{6} See Duffy & Ferrari, supra note 3.
\textsuperscript{7} See Duffy & Ferrari, supra note 3.
\textsuperscript{8} See Duffy & Ferrari, supra note 3.
\textsuperscript{9} See Duffy & Ferrari, supra note 3.
\textsuperscript{10} See Duffy & Ferrari, supra note 3.
\textsuperscript{11} F. DeLorenzo et al., supra note 4.
\textsuperscript{12} See Duffy & Ferrari, supra note 3.
\textsuperscript{13} P.M. Ridker et al., Long-term, Low-intensity Warfarin Therapy for the Prevention of Recurrent Venous Thromboembolism, 48 NEW ENG. J. MED. 1425, 1425-1434 (2003); See Delorenzo et al., supra note 4.
\textsuperscript{14} See DeLorenzo et al., supra note 4.
\textsuperscript{15} See DeLorenzo et al., supra note 4.
\textsuperscript{16} See DeLorenzo et al., supra note 4.
aggregation. The administration of anticoagulants presents numerous complicated risks due to its link with excessive bleeding and other complications. With respect to Warfarin, the most commonly used anticoagulant, it has been estimated that fifteen percent of patients experience idiopathic bleeding upon administration, with three-and-a-half percent suffering a fatal hemorrhagic event. In fact, Warfarin is second only to insulin in rate of adverse outcomes upon administration. Yet, in some instances, anticoagulation therapy can actually induce thrombosis rather than bleeding. For example, the administration of heparin can manifest as an adverse immune response, meaning that platelets aggregate and form a clot. Consequently, anticoagulation therapy demands rigorous clinical management.

**Background**

**Litigation Involving Anticoagulants: A Growing Trend**

Adverse response to anticoagulation treatment is a frequent source of litigation in the United States. For example, in *Bella v. Turner* a patient filed a medical malpractice action against her primary attending physician, a cardiologist, and the medical clinic with which he was associated. The Plaintiff appeared to be suffering from a heart attack when she sought treatment from the medical clinic where the cardiology attending performed an angioplasty and administered the anticoagulant drug heparin to reduce the risk of blood clotting. The plaintiff remained on heparin for five

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18 *Id.*
19 *Id.*
20 *Id.*
22 *Id.*
23 See, e.g., Clark v. HCA, Inc., 210 S.W.3d 1, 7 (Tex. App. 2005) (upholding dismissal of plaintiff’s claim based on administration of anticoagulants despite contraindications for failure to proffer sufficient expert report of breach of the standard of care); see also Berlin v. Cleveland Clinic Found., 2005 WL 1926049 ¶ 47 (Ohio App. 2005) (slip opinion) (reversing lower court’s directed verdict in favor of physician and hospital where plaintiff sued for bleeding and anemia caused by anticoagulants and holding, in part, that expert opinion stated a *prima facie* case as to proximate cause); see also Forrest County Gen. Hosp. v. Kelley, 914 So. 2d 242, 244 (Miss. 2005) (considering statute of limitations in an action predicated on brain hemorrhage and bleeding caused by administration of heparin).
25 *Id.*
days, and was then discharged. However, the following day, the plaintiff returned to the hospital, having suffered a stroke. Other physicians treated her and administered heparin, and the defendant cardiologist resumed the care of the plaintiff and continued to prescribe heparin. About two weeks later, the plaintiff suffered a second stroke. Her family requested a new cardiologist, who promptly ordered a hematology consult. The hematologist diagnosed the plaintiff with heparin-induced thrombocytopenia with thrombosis (HITT).

Two theories of the resulting malpractice action emerged. First, the plaintiff contended that the administration of heparin caused her blood to clot secondary to HITT, resulting in an ischemic stroke. Secondly, she argued that heparin was inappropriate for a patient prone to HITT. The defendants, on the other hand, contended that the plaintiff suffered from antiphospholipid antibody syndrome (APLAS), another blood disorder, and that APLAS caused the stroke, and additionally that heparin is appropriate for patients with APLAS. Ultimately, a jury awarded the plaintiff one million dollars against both defendants.

Naturally, the defendants appealed on numerous grounds. Firstly, they contended that the trial court erred by preventing the defendants from cross-examining the plaintiff's two experts who found no fault with the succeeding cardiologist (not a defendant in the case). The succeeding cardiologist, as well as numerous other treating physicians, like the defendant cardiologist, did not diagnose HITT and did not discontinue heparin. Essentially, the defendants asserted that the inability to cross-examine the plaintiff's experts kept them from cross-examining the physicians "on matters of objectivity and credibility, and prevented [the] defendants from

26 Id.
27 Id. at 894.
28 See id. at 898.
30 Id.
31 Id.
32 Id.
33 Id.
35 Id at 895-96.
36 See Bella, 30 S.W.3d at 895 (describing that pursuant to the state's limitations on non-economic damages, Judge Holden of the lower Missouri Circuit Court entered a lesser judgment in favor of the patient).
37 Id.
38 Id.
39 Id.
developing testimony refuting a key component of [the] plaintiff's case-in-chief, namely that HITT was a common and well-known diagnosis..."40

Ultimately, the court concluded that there was no error as to this point raised.41 Generally, courts have ruled that evidence of the negligence of other persons not on trial is inadmissible.42 Furthermore, “where concurrent or successive negligence combined together results in injury, the injured party may recover damages of either or both, and neither can use the defense that the prior occurrence or negligence of the other contributed to the injury.”43

The defendants' other points raised were similarly denied.44 Specifically, the defendants were not allowed to make an adverse inference from the plaintiff's failure to call the succeeding physician and consulting hematologist because there was no error resulting from the disjunctive verdict director that the defendant cardiologist failed to order a hematology consult in a timely manner. Additionally, there was no abuse of discretion in failing to declare a mistrial when the plaintiff's expert stated that negligence was “so gross” that it was “irresponsible” for him not to get involved. Finally, an attempt by a qualified neurologist to give expert testimony failed, despite this neurologist's having diagnosed and treated HITT in the past.45 While the molecular genetics of the plaintiff's response to anticoagulants remains a mystery, the verdict was upheld and stands as an example of a growing trend in cardiac and neurologic malpractice.46

41 Id. at 896.
42 Id.
43 Id.
44 Id.
45 Id.
Molecular Epidemiology of Clotting Response and the Pharmacogenetics of Anticoagulants

While anesthesiologists have long been aware that individual difference in patient response to anesthesia plagues the treatment regimen, studies of genetic variation in anticoagulation response are in their infancy. Scientists recognize that despite population-based differences in clotting response, the molecular mechanism underlying these differing responses has been poorly understood. For example, Alaska natives rarely experience deep vein thrombosis post-operatively. And it has long-been recognized that Inuits exhibit a significantly longer clotting time than continental European populations and Anglo-Americans. Furthermore, mortality from cardiovascular events is rare in this population. Some theorize that blood clotting serves a critical evolutionary advantage and, for this reason, clotting response varies among individuals and especially across ethnicity. Given the Inuits’ staple diet of fish and whale blubber, perhaps the likelihood of heart attack due to a blood clot was a more immediate threat than death from hemorrhaging. Therefore, the Inuits may have adapted with longer bleeding times and reduced platelet aggregation. However, scientists have long-recognized that environmental factors also play a critical role. Fatty acids found in fish oil, apparently converted in the cardiovascular system to an anti-platelet aggregation compound, reduce thrombolytic events, including MI. Increasingly, clinical and molecular researchers are finding that pharmacogenetic factors

\[ \text{Hosp., 2005 WL 880987 (Cal.App. 1 Dist.); Hargroder v. Unkel, 888 So.2d 953 (La.App. 2 Cir. 2004); Crenshaw v. County of Los Angeles, 2004 WL 938397 (Cal.App. 2 Dist.).} \]
\[ \text{Id. at 298. See also Mihai V. Podgoreanu & Debra A. Schwinn. New Paradigms in Cardiovascular Medicine: Emerging Technologies and Practices: Perioperative Genomics. 46 J AM. COLL. CARDIOL. 1965-1977 (2005).} \]
\[ \text{T. Rosenzweig, Post-Operative Deep Vein Thrombosis is Infrequent in Alaska Native. 62 INT. J. CIRCUMPOLAR HEALTH 388-396 (2003).} \]
\[ \text{See S. Fischer, P.C. Weber & J. Dyerberg, The Prostacyclin/Thromboxane Balance is Favorably Shifted in Greenland Eskimos, 32 PROSTAGLANDINS 235-41 (1986); J. Dyerberg & H.O. Bang, Haemostatic Function and Platelet Polyunsaturated Fatty Acids in Eskimos, 2 LANCET 433-35 (1979); J. Dyerberg & H.O. Bang, Lipid Metabolism, Atherogenesis, and Haemostasis in Eskimos: The Role of the Prostaglandin-3 Family, 8 HAEMOSTASIS 227-233 (1979).} \]
\[ \text{See Fischer, supra note 50, at 235-41.} \]
\[ \text{See Fischer, supra note 50, at 235-41.} \]
\[ \text{See Fischer, supra note 50, at 235-41.} \]
\[ \text{See Fischer, supra note 50, at 235-41.} \]
\[ \text{See Fischer, supra note 50, at 238.} \]
\[ \text{See Fischer, supra note 50, at 238.} \]
are at the root of adverse or variable patient response to anticoagulation therapy.\textsuperscript{57}

Inherited differences in drug response fall into three categories: 1) pharmacokinetic, 2) pharmacological, and 3) physiological.\textsuperscript{58} Pharmacokinetic biochemical pathways involve the metabolism and excretion of the drug.\textsuperscript{59} Genes involved in this pathway relate to metabolic and transporting enzymes.\textsuperscript{60} Pharmacological pathways involve gene products as proteins that bind to the drug.\textsuperscript{61} Finally, physiological pathways involve homeostatic mechanisms, such as blood clotting enzymatic cascades.\textsuperscript{62} Genetic variability appears to be a source of variable response to anticoagulants.\textsuperscript{63} Genetic variation as to molecular complexes involved in blood clotting may explain wide variability as to hemorrhagic and thrombolytic complications.\textsuperscript{64} Clinical studies show that blood clotting involves a complex system of regulation and expression of multiple genes, and therefore, a wide range of genetic factors could be responsible for adverse drug reactions to anticoagulation therapy.\textsuperscript{65} Environmental factors that interact with genetic predisposition may also contribute to hemorrhagic and thrombolytic events.\textsuperscript{66}

The molecular mechanisms underlying many traits have been established, but only recently, through diligent research of the human genome and concomitant improvements in biotechnological methods have scientists gleaned any inkling as to the wide genetic variation underlying disease, especially those involving multiple genes and environmental factors.\textsuperscript{67} HITT is but one example.\textsuperscript{68} HITT is an autoimmune disorder that manifests as thrombocytopenia.\textsuperscript{69} One course of pathophysiology involves the binding of a heparin-dependant antibody to a platelet factor and heparin and the simultaneous interaction of antibody with a platelet antibody receptor.\textsuperscript{70} This complex

\textsuperscript{57} Fox et al., \textit{supra} note 47, at 297.  
\textsuperscript{59} Id.  
\textsuperscript{60} Id.  
\textsuperscript{61} Id.  
\textsuperscript{62} Id. at 758.  
\textsuperscript{63} Rojas et al., \textit{supra} note 17, at 389.  
\textsuperscript{64} Id.  
\textsuperscript{65} Rojas et al., \textit{supra} note 17, at 389.  
\textsuperscript{66} Fox et al., \textit{supra} note 47, at 389.  
\textsuperscript{67} Id.  
\textsuperscript{68} Fox et al., \textit{supra} note 47, at 390.  
\textsuperscript{69} Fox et al., \textit{supra} note 47, at 394.  
\textsuperscript{71} See Fox, \textit{supra} note 47, at 315. The disease pathway of one type of HITT involves the binding of a heparin-dependent type G immunoglobin (IgG) to a compound called platelet factor 4
series of events results in activation of blood platelets and injury to the single layer of smooth cells in the vasculature resulting in thrombocytopenia and, at times, thrombosis. Platelet factor continues to be released resulting in further mobilization of this enzymatic cascade and more antibody binding and platelet activation.

Studies show that one quarter to one half of patients undergoing cardiac surgery have detectable heparin-dependant antibodies within five to ten days after surgery. Yet, only between one and three percent of these patients who have received heparin post-operatively develop HITT. Of that small percentage, only a fraction experience thrombolytic complications. Why some patients with heparin-dependant antibodies develop severe thrombolytic complications, and others do not, has yet to be understood. Molecular genetic studies of the role of certain molecular machinery involved in HITT have been inconsistent. Some studies isolated an association between certain genotypes and phenotypes, but genotypes widely vary. Scientists (PF4), as well as the drug heparin. The IgG interacts with a platelet immunoglobin receptor resulting in platelet activation and injury to the blood vessel's epithelium, leading to thrombocytopenia and sometimes thrombosis. Specifically, a portion of the heparin-dependant IgG binds to the so-called PF4-heparin complex which resides on the surface of mobilized blood platelets. As a result, another portion of the bound IgG "cross-links" to receptors of nearby aggregating platelets, resulting in still further platelet activation. Fox, supra note 47. Additionally, PF4 is released from the platelets, fueling further PF4-heparin complex production and further antibody binding. Id. See Fox, supra note 47, at 297-315. See Fox, supra note 47, at 297-315.


Id. at 129-47.


See id. (explaining how the platelet receptor, known to bind IgG, and, in turn, induces platelet activation, has been targeted by geneticists studying HITT). Four different genetic markers give rise to changes in its protein structure. Carlsson, supra note 76, at 1526-35. Therefore, several genetic markers could be responsible for a protein structure that alters the number of receptors on a blood platelet's surface. Id.

admit it is plausible that varied research results reflect some unidentified environmental influences on the pathophysiology of HITT.79

As researchers gain a clearer understanding of the molecular biological reasons that explain why seemingly similar patients can exhibit radically different clinical outcomes, risk assessment for adverse outcomes, such as thrombolytic events, may begin to include identification of genetic markers.80 At least one major biotechnology company has marketed a test capable of identifying genetic variations as to drug metabolizing enzymes.81 This pharmacogenomic test accurately predicts enzymatic activity associated with certain genetic markers.82 There are two major obstacles that hamper progress in predictive genomics.83 One major obstacle to accurate prediction of clinical outcome is the fact that diseases, such as atherosclerosis, which complicate the clinical picture, involve a myriad of genetic and environmental factors whose interaction is unique to the individual.84 Thus, establishing a patient’s genetic profile is only clinically useful in part.85 Animal models are enabling researchers to determine genes and molecular pathways that are activated under certain environmental stressors and serve some evolutionary advantage.86 A second major obstacle is that the amount of time it takes to obtain a genotype from a blood sample may not be realistic under certain circumstances.87 Overall, genetic testing is expected to lead to better monitoring of drug response and individualized selection of dosing.88


79 Fox, et al., supra note 47.
81 Id.
82 Id.
83 Id.
84 Podgoreanu, et al., supra note 80.
85 Podgoreanu, et al., supra note 80.
86 Podgoreanu, et al., supra note 80.
87 Podgoreanu, et al., supra note 80.
88 Podgoreanu, et al., supra note 80.
Analysis

Addressing Physician Liability: Predictive Genomics and Informed Consent

Genetic variability in clotting response may be at the root of a flurry of litigation. Physicians may be unaware that a particular patient is genetically predisposed to a hemorrhagic or thrombolytic event secondary to anticoagulation therapy. Physicians also may not be equipped with information concerning intervening environmental factors that may contribute to a hemorrhagic or thrombolytic event.

Gaining a better understanding of the pharmacogenetics of anticoagulation medication may impact physician liability. Information regarding genetic variability could decrease litigation involving anticoagulants in two ways. First, pharmacogenetics may ultimately prove instrumental in decreasing physician liability. The use of predictive genomics could be used to identify a patient’s genotype prior to treatment in order to exclude those who will be harmed by heparin or another anticoagulant. Physicians could, in turn, produce more optimal treatment decisions which would be less likely to result in malpractice claims. Second, physicians could incorporate information regarding genetic variability into informed consent protocols. Physicians are only under a duty to disclose risks that are material. Generally speaking, a physician has a duty of care to a patient to obtain a voluntary, informed consent which typically includes: 1) the general nature of the contemplated therapy; 2) the risks involved; 3) the prospects of success; and 4) any alternative methods of achieving the same treatment goal. Physicians should synthesize knowledge regarding complex inheritable and environmental interactions to inform patients of the possibility of an idiosyncratic reaction to anticoagulation therapy. At least one pilot study regarding disclosure of the risk of HIT secondary to heparin therapy, in particular, has shown that patients who adjudged the risk to be material, were able to comprehend the risk and were not dissuaded from treatment. Genomic profiling leads to a heightened ability to identify patients vulnerable to adverse outcomes and renders physicians better able to identify and subsequently disclose risks. Indeed, predictive genomics could serve to narrow the gap between patients’ and doctors’ perceptions of risk. While the medical community is most concerned with statistical probability in assessing risk, patients themselves tend to attach materiality to those risks. Predictive genomics will enable physicians to tailor risk disclosers to the

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90 See, e.g., Lee Ross & Donna Shestowsky, Contemporary Psychology’s Challenges to Legal Theory and
statistical outliers, not just to the general therapeutic population. Importantly, physicians will not be 100 percent accurate in predicting patient outcomes. Physicians will have to make clear that patients categorized as low-risk for adverse outcome via genomic testing are not in a no-risk grouping.

Summary and Conclusion

Acute myocardial infarction is the main cause of mortality among Western countries. The final physiologic process of atherosclerotic evolution, supporting development and progression of cardiovascular diseases, is thrombosis. Anticoagulation treatment has proven tremendously important in prevention and treatment of acute clotting incidents, including stroke, and deep venous thrombosis. Nevertheless, anticoagulation therapy can manifest as an adverse clinical outcome, as a result of a hemorrhagic event or inappropriate platelet aggregation. Adverse response to anticoagulation treatment is a frequent source of litigation in the United States. Blood clotting serves a critical evolutionary adaptive advantage, and for this reason, clotting response may vary across ethnicity. Increasingly, clinical and molecular researchers are finding that pharmacogenetic factors are at the root of adverse or variable patient responses to anticoagulation therapy. Genetic variability may be a source of variable responses to anticoagulants. Environmental factors that interact with genetic predispositions may contribute to hemorrhagic events. Predictive genomics may ultimately prove instrumental in decreasing physician liability, by improving clinical outcomes and enabling physicians to individualize risk disclosers while obtaining informed consent.

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