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Personalized Medicine and Patient Privacy Concerns in the Telemedicine Age

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It is an ancient tradition in medical practice that a patient's confidences must be respected and unauthorized disclosure of medical information be prohibited.[3] This practice has become progressively more difficult to maintain as patients' medical information has become collected in electronic media, which can be inherently more difficult to adequately secure.[4] Complicating traditional privacy concerns is the extent of disclosure required by insurers (both public and private) to justify and coordinate coverage for medical care.[5] This paper reviews efforts taken to date and on-going to enhance protection for medical information, particularly with regard to electronic databases containing such information. It also reviews trends in medical diagnostics and protections for such methods, in the face of judicial, policy, and public enmity towards restrictions thereof.

1. Medical records privacy

The principal Federal law protecting patient privacy in their medical records is the

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[3] "Whatsoever things I see or hear concerning the life of men, in my attendance on the sick or even apart therefrom, which ought not be noised abroad, I will keep silence thereon, counting such things to be as sacred secrets." *See Greek Medicine: The Hippocratic Oath*, U.S. NAT'L LIB. OF MED. (2012), https://www.nlm.nih.gov/hmd/greek/greek_oath.html.

[4] Feisal Nanji, *Security Challenges of Electronic Medical Records*, COMPUTERWORLD (Feb. 19, 2009), https://www.computerworld.com/article/2531320/security0/security-challenges-of-electronic-medical-records.html.

[5] *See Improved Care Coordination: The Need for Better Improved Care Coordination*, HEATHIT.GOV, (Mar. 20, 2014), https://www.healthit.gov/providers-professionals/improved-care-coordination.

Health Insurance Portability and Accountability Act of 1996, or HIPPA.[6] This Act provides national standards for electronic health care transactions and, having been enacted prior to digitalization of most medical records was initially concerned with the accessibility of medical records tied to reimbursement.[7] The law is administered under the Office of Civil Rights for HIPAA as part of the U.S. Department of Health and Human Services[8] and also codifies responsibility for maintaining the confidential status of patient electronic medical records.[9]

With the advent of electronic medical record-keeping and "telemedicine," HIPAA requires a clinician involved in telemedicine has the same duty to safeguard a patient's medical records and keep their treatments confidential as a traditional physician.[10] Operationally, this involves ensuring that both the place confidential information resides and where it is stored must be secure and no confidential patient information exposed inadvertently or otherwise.[11] This is particularly relevant due to the potential for such exposure, particularly by technical personnel who can act more independently of the medical team than in traditional medical settings (where the records are conventionally kept on-site in a physician's office or hospital records repository with all the attendant security related to other aspects of the practice such as access to drugs). In addition and unique to electronic medical record keeping, a patient's confidential medical information

[6] Health Insurance Portability and Accountability Act ("HIPAA") of 1996, Pub. L. No. 104-191, 110 Stat. 1936 (1996).
[7] 42 U.S.C. § 1320a-7c (2010).
[8] U.S. Dep't of Health & Human Serv., https://www.hhs.gov/ocr/index.html.
[9] 42 U.S.C. § 1320a-7c (2010).
[10] 45 C.F.R. § 160.202 2007.
[11] 42 U.S.C. § 1320a-7c (2010).

is subject to potential exposure from hackers during transmission or storage;[12] this risk requires at a minimum some form of encryption to prevent information from being inappropriately accessed.[13]

The law identifies three groups of individuals who have responsibility for maintaining the confidentiality of patient medical records and other information:

- A covered healthcare provider, who is a person, business or agency that furnishes, bills, or receives payment for health care in the normal course of business and transmits any covered transaction electronically[14]

- A health care clearinghouse, which is a business or agency that processes or facilitates the processing of health information from a nonstandard format or content into a standard format or vice versa, or the business or agency performs this function for another legal entity[15]

- A private benefit plan, which is a plan for an individual, group or some combination thereof, and provides or pays for the cost of medical care, having greater than 50 participants and that is not self-administered[16]

Also included under the umbrella of HIPAA responsibility for maintaining patient confidentiality are "business associates," which comprise anyone that:

- Creates, receives, maintains, or transmits protected health information (PHI) to perform certain functions or activities on behalf of a covered entity;

- Provides legal, actuarial, accounting, consulting, data aggregation, management, administrative, accreditation, or financial services to, or for, a covered entity in situations where PHI is involved;
- Provides data transmission services to a covered entity and has access to PHI on a routine basis;

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[12] U.S. Dep't. of Health & Human Serv. (2013), https://www.hhs.gov/hipaa/for-professionals/security/laws-regulations/index.html.
[13] *See* Elizabeth Snell, *Breaking Down HIPAA: Health Data Encryption Requirements*, HEALTHITSECURITY.COM (Mar. 20, 2015), https://healthitsecurity.com/news/breaking-down-hipaa-health-data-encryption-requirements.
[14] HIPAA § 262, 42 U.S.C. §§1320 d(3), 1320d-1.
[15] HIPAA § 262, 42 U.S.C. §§1320 d(2), 1320d-1.
[16] HIPAA § 262, 42 U.S.C. §§1320 d(5), 1320d-1.

- Offers personal health records to one or more individuals on behalf of a covered entity; and/or

- Operates as a subcontractor of the business associate who has been delegated a function, activity, or service in a capacity other than as a member of the business associate's workforce.[17]

2. Genetic information privacy

A particular facet of patient information related to health and subject to inadvertent disclosure is genetic information, which has become available and greatly increased in scope over the past 40 years.[18] Today there are many more examples of diseases having a known genetic basis as well as diseases where the risk (and especially increased risk) of developing such diseases is being elucidated.[19] Concerns that this information could be used to discriminate against individuals in employment or other social contexts (including access to health insurance) motivated passage of the Genetic Information Nondiscrimination Act (GINA) in 2008.[20] The Act prohibits health insurers or health plan administrators from requesting or requiring genetic information of an individual or the individual's family members, or using it for decisions regarding coverage, rates, or preexisting conditions.[21] The law also prohibits most employers from using genetic

[17] *See* 45 C.F.R. §§ 164.502(e), 164.504(e).
[18] Previously, only a handful of illnesses and propensities were known to have a genetic basis. These include diseases related to chromosomal abnormalities, such as Down's Syndrome, Turner's Syndrome, and Klinefelter's syndrome, and those related to genetic mutations, including sickle cell anemia, cystic fibrosis, Duchenne's muscular dystrophy, and Tay-Sachs disease. *See* H. Chial, *Rare Genetic Disorders: Learning About Genetic Disease Through Gene Mapping, SNPs, and Microarray Data*, 1 NATURE EDUC. 192 (2008).
[19] These diseases include (most (in)famously) increased risk for breast and ovarian cancer associated with mutations in the BRCA gene, as well as Huntington's chorea and familial adenomatous polyposis.
[20] Pub. L. 110-233, 122 Stat. 881 (2008).
[21] *Id*.

information for hiring, firing, or promotion decisions, and for any decisions regarding terms of employment.[22] GINA's health coverage non-discrimination protections do not, however, extend to life insurance, disability insurance and long-term care insurance,[23] nor does the Act mandate coverage for any particular test or treatment.[24] The size of a company also limits access to GINA protections: GINA's employment provisions generally do not apply to employers with fewer than 15 employees.[25] The impact on GINA for health coverage is limited, and the law is aimed primarily at protecting individuals from discrimination based on their genetic heritage.[26] This is important because GINA does not prohibit health insurers or health plan administrators from obtaining and using genetic test results in making health insurance payment determinations (which could form an economic basis for such discrimination).[27]

3. Further protections based on technological developments

As technology has developed the capacity and propensity for new and unexpected vulnerabilities for patients' confidential health information have increased concomitantly.

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[22] *Id*.; there can be exceptions where a genetic condition or propensity is directly related to an individual's ability to perform the tasks required for the job.
[23] *Id*.
[24] *Id*.
[25] *Id*.
[26] Genetic Information Nondiscrimination Act of 2008, Pub. L. No. 110-233, 122 Stat. 881 (2008); For example, for health coverage provided by a health insurer to individuals, GINA does not prohibit the health insurer from determining eligibility or premium rates for an individual based on the manifestation of a disease or disorder in that individual. For employment-based coverage provided by group health plans, GINA permits the overall premium rate for an employer to be increased because of the manifestation of a disease or disorder of an individual enrolled in the plan, but the manifested disease or disorder of one individual cannot be used as genetic information about other group members to further increase the premium.
[27] *Id*.

Accordingly, Congress has seen fit to expand legal protections for patient health records; the most recent example of such laws is the Health Information Technology for Economic and Clinical Health Act of 2009 (the HITECH Act).[28] This Act provides subsidies for using/creating electronic health records and expands privacy and security provisions of HIPAA.[29] These HIPAA expansions include direct regulation of business associates (as defined under HIPAA) and application of HIPAA's privacy and security rules to such entities.[30] The HITECH Act also dramatically increases the required response to breaches of PHI and the enforcement of such requirements, including notification, patient access to information regarding breaches to the confidentiality of their records, and civil and criminal penalties, where appropriate, for breach.[31]

Compliance with these various statutes is not something intrinsic to electronic medical record-keeping systems but is exquisitely dependent on how they are implemented. In assessing compliance (or designing systems to ensure compliance), it is important to distinguish having information that identifies patients for some purposes (such as billing, diagnosis, or treatment) but not for others (disclosing personal information outside the scope of patient confidentiality). Efforts to ensure compliance include agreements (ultimately, contracts) between medical personnel (doctors, nurses, other practitioners) who generate medical information and technical actors (database administrators and technical personnel), wherein the parties acknowledge their

[28] American Recovery and Reinvestment Act of 2009, Pub. L. No. 111-5, 123 Stat. 226 (2009).
[29] *Id*. at Subtitle C.
[30] *Id*. at Subtitle D.
[31] *Id*.

responsibilities and agree to behave in a HIPAA-compliant manner.[32] The existence of such agreements can raise awareness amongst all actors involved in producing and cataloging patient health information, and can avoid *post-hoc* claims of inadvertence while ensuring appropriate ascribing of liability for data breach (and perhaps minimizing the likelihood that breach and liability for breach will ensue). These efforts are important because personal health information disclosure is often irremediable to all parties.

4. Privacy concerns

Personal medical health records fall well within the modern expansion of privacy protected under the First Amendment,[33] as well as under interpretations (conventional as well as modern) of the Third, Fourth, Fifth, and Fourteenth Amendments.[34] Given the intimate nature of medical information, these privacy concerns, a patient's medical records and other health information involve equivalent concerns regarding protections against publicity of this information as motivated protection of other areas of individual privacy. These protections are frankly directed to a citizen's protection from government intrusion, however. Protections from private actors (including employer and the press, among others) must rely on other power of Congress, such as its power over interstate commerce. This type of interest certainly applies to the use of medical information regarding employment and, particularly in view of nationwide insurance providers (despite local control thereof state-by-state) and similar consolidation of the medical provider industry (hospitals, for

[32] Ultimately, of course, such agreements have their greatest impact on how blame for medical records data breaches are assessed, but having the agreement itself can raise awareness of the risks and responsibilities involved.
[33] *See Griswold v. Connecticut*, 381 U.S. 479 (1965).
[34] All these amendments more or less directly implicate the privacy right for an individual to be secure in her home or in her possessions and to restrict the government's ability to intrude on that privacy by requiring due process of law to do so.

example). These privacy rights can be functionally if not legally limited when pitted against free speech and press freedom rights under the First Amendment; remedies for unauthorized disclosure in such cases may be cabined within traditional libel, slander, rights of publicity and breach of confidentiality actions (albeit these will be more attenuated for individuals who have purposefully placed themselves in the public eye, such as actors, musicians, and other artists, as well as politicians).[35]

5. Ownership of patient medical record databases

Patient medical information is contained in electronic databases. Even in the analog age, there was a recognition that the accumulation of individual items of data in a collection was not only valuable but could be protected as a form on intellectual property.[36] Books of telephone listings and maps (particularly for cities and towns) could be protected by copyright, and more particularized lists (such as a company's client or customer lists) were valuable trade secrets.[37] The value of this type of intellectual property was not in its individual items but in the collection; in this way such traditional databases (which is what we would recognize them to be, especially when reduced to electronic media) differ from collections of patient medical information, in which each item represents a person's

[35] *See New York Times Co. v. Sullivan*, 376 U.S. 254 (1964).
[36] *See* Julie E. Cohen & William M. Martin, *Intellectual Property Rights in Data*, INFO. SYS. & THE ENV'T (2001), https://www.nap.edu/read/6322/chapter/5. Protecting databases has traditionally not been a particularly attractive option, because among other things it relied on trade secret legislation enacted state-by-state. This changed when Congress enacted the Defend Trade Secrets Act in 2016 (Pub. L. 114-153, 130 Stat. 376 (2016), *codified at* 18 U.S.C. § 1836 *et seq*.); *see also* Josh Rich, *President Obama Signs Defend Trade Secrets Act*, PATENT DOCS (May 11, 2016), http://www.patentdocs.org/2016/05/president-obama-signs-defend-trade-secrets-act.html#comments.
[37] *See* Timothy K. Sendek, *Customer Lists as Trade Secrets*, NAT'L L. REV. (Dec. 30, 2009), https://www.natlawreview.com/article/customer-lists-trade-secrets.

medical history and (in some instances) propensity for developing a disease.[38] The technology involved in creating or storing information (either *per se* or related to physical samples) can be protected (by patenting[39] or less productively as a trade secret[40]).[41] But databases themselves are difficult to protect because each new entry creates a new database not described before.[42]

Like traditional trade secret collections, protecting medical information databases involves restricting access, which is the key property right.[43] This can be limited to interrogating a portion or subset of the items in the database or can provide have access to the entirety of the information therein.[44] One of the negative consequences of such protection can be academic research, insofar as the database owner restricts access.

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[38] This value being demonstrated by the protections for these items as discussed above; Sendek, *supra* note 37.

[39] Patenting and trade secret protection are not necessarily mutually exclusive. Most inventions are kept confidential (*i.e.*, are trade secrets) until a patent application is published. Moreover, a product can have some aspects patented and others kept as trade secrets (provided the best mode requirement of 35 U.S.C. § 112(a) is not violated); *See Christianson v. Colt Indus. Operating Corp.*, 486 U.S. 800 (1988).

[40] Although trade secret protection can lead to substantial judgments. *See, e.g.*, *Epic Systems Corp. v. Tata Consultancy Servs., Ltd.*, No. 14-cv-748-wmc, 2016 U.S. Dist. LEXIS 50157 (W.D. Wis. Apr. 14, 2016) ($240 million compensatory damages, $700 million punitive damages); *GM v. Ignacio Lopez de Arriortua*, 948 F. Supp. 656 (E.D. Mich. 1996) ($1.1 billion judgment: $100 million cash, $1 billion products); and *Pacesetter v. Nervicon*, No. BC424443 (Cal. Superior Ct. 2011) ($947 million judgment).

[41] *See* USPTO Classification Schedule, Class 707, Subclasses 600-831 (Jan. 2010), https://www.uspto.gov/web/patents/classification/uspc707/sched707.htm.

[42] Each iteration of a database created by adding a new entry creates a new database and thus, defeats an applicant's ability to satisfy at least the written description requirement of 35 U.S.C. § 112(a). *See*, by analogy, *In re Alonso*, 545 F.3d 1015 (Fed. Cir. 2008).

[43] This is true even for collections of biological samples or organisms (which are often individually not patentable) such as those curated by the American Type Culture Collection (www.atcc.org).

[44] This is true whether the collection is physical (such as biological or other specimens) or just lists (pure information).

Fortunately, this rarely happens.[45]

6. The uncertain future of patent protection for human diagnostics

One advantage of accumulating databases of patient medical information is that, with sufficient size, patterns of relationships on inheritance[46] or environmental exposure[47] can become evident. This has been the experience of the past 40 years, particularly with regard to identifying genes (and in particular genetic mutations or other variants) that are involved with and provide predictive power for certain diseases.[48] The continued

[45] An example of how database access can provide competitive advantages even without patent protection is the Myriad Genetics database for BRCA gene mutations. As is well known, Myriad's patents on isolated human BRCA genes *BRCA1* and *BRCA2* were invalidated by the Supreme Court in 2013. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013), and patent protection for methods of detecting such mutations lost when the Court of Appeals for the Federal Circuit invalidated such claims on appeal from consolidated actions for infringement brought by Myriad against several genetic diagnostic providers in the wake of the Supreme Court decision. *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755 (Fed. Cir. 2014). Nevertheless, Myriad has been able to protect its competitive advantage in the BRCA testing market because its extensive database (estimated to contain the results from more than 3 million patients) enables Myriad to provide informative diagnostic information with regard to genetic variants that occur with sufficient infrequency (termed "variants of unknown significance" or "VUS") that their association with predicted disease is unclear without reference to Myriad's database.

[46] Indeed, one advantage University of Utah researchers enjoyed in the competition between several laboratories to isolate the human BRCA genes was the records, going back more than 100 years, of death and causes of death for generations of ancestors. Because breast and ovarian cancers were well recognized during this time period, classical genetic methods could be combined with modern molecular biological approaches to identify the portions of chromosome 17 (BRCA1) and chromosome 13 (BRCA 2) where these loci could be found. *See*, Jeff M. Hall et al., *Linkage of early-onset familial breast cancer to chromosome 17q21*, 250 SCIENCE 1684–1689 (1990); Richard Wooster et al., *Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13*, 265 SCIENCE 2088–90 (1994).

[47] *See*, John B. Whitfield et al., *Genetic Effects on Toxic and Essential Elements in Humans: Arsenic, Cadmium, Copper, Lead, Mercury, Selenium, and Zinc in Erythrocytes*, 118 ENVTL. HEALTH PERSP. 776, 776-82 (2010).

[48] *For example*, the BRCA genes for breast and ovarian cancer (U.S. Patent Nos. 5,747,282 and 5,837,492); repetitive motif expansion in Duchenne's muscular dystrophy

accumulation of this evidence is expected (and intended) to result in individual-centric medicine (termed "personalized medicine"), *i.e*., by knowing an individual's genotype for genes involved in disease or treatment of disease will permit treatment of the individual rather than what has been developed for a population.[49]

Many of these diagnostic methods have been heretofore the subject of patent protection.[50] Patents, in the U.S., are defined by statute; this includes what types of inventions are eligible for patenting, which is codified in the patent statute under Section 101.[51] Until recently this statutory requirement has been construed broadly to include "anything under the sun made by man."[52] However, the scope of patent subject matter eligibility has always been constrained by exceptions recognized by the Supreme Court;

(M. Koenig et al., *The complete sequence of dystrophin predicts a rod-shaped cytoskeletal protein*, 53 CELL 219, 219–26 (1988); M. Koenig et al., *The molecular basis for Duchene versus Becker muscular dystrophy: correlation of severity with type of deletion*. 45 AM. J. HUMAN GENET. 498, 498–506 (1989)) and Fragile X syndrome (Kathryn B. Garber et al., *Fragile X syndrome*, 16 EUROPEAN J. OF HUMAN GENETICS 666, 666–72 (2008)); and deletion of a specific amino acid (Phe_{508}) in cystic fibrosis (J.M. Rommens et al., *Identification of the cystic fibrosis gene: chromosome walking and jumping*, 245 SCIENCE 1059, 1059-65 (1989)).

[49] "[T]herapy with the right drug at the right dose in the right patient." Laviero L. Mancinelli et al., *Pharmacogenomics: The Promise of Personalized Medicine*, 2 AAPS PHARMSCI 29, 29-41 (2000). Personalized medicine is expected to provide the ability to make more informed medical decisions and result in a higher probability of desired outcomes thanks to better-targeted therapies and a reduced probability of negative side effects. Unlike in traditional medicine, personalized medicine is focused on prevention and prediction of disease rather than reaction to it and earlier disease intervention than has been possible in the past. Another expected benefit is to reduce healthcare costs.

[50] *See* U.S. Patent Nos. 5,747,282 (BRCA 1); 5,837,492 (BRCA 2); 5,187,063 (Duchenne's muscular dystrophy); and 6,107,025 and 6,180,337 (Fragile X syndrome), among others.

[51] "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101.

[52] *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980).

these are "laws of nature, physical phenomena, and abstract ideas."[53]

With regard to claims to diagnostic methods, they adopt a canonical format of reciting steps to "determine and infer": one or more steps involve detecting something (*e.g.*, a biomarker) and from that inferring something related to what is detected (*e.g.*, the presence or absence of a disease).[54] As a consequence, unlike industrial and chemical method claims,[55] diagnostic methods claim to produce information, *i.e.*, the inference related to what is detected.[56] In addition, for medical diagnostics claims, patent protection implicates public policy concerns involving whether permitting patenting will inhibit the practice of medicine or interfere with a physician treating a patient as a result of obtaining a diagnostic result.[57]

These concerns apparently prompted a series of decisions by the U.S. Supreme Court severely restricting patent eligibility to medical diagnostic methods.[58] These decisions mandate that claims that merely recite a law of nature and supply the direction to "apply it" are not patent eligible.[59] The law as interpreted by the Court requires the claim to recite (and the specification to disclose) "something more" than the law of nature, and that "something more" must be more than what is "well-understood, routine, and

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[53] *Id*.
[54] Kevin Emerson Collins, *Prometheus Laboratories, Mental Steps, and Printed Matter*, 50 HOUSTON L. REV. 391, 394 (2013).
[55] The practice of these types of method claims produce a device or other tangible product; *see Diamond v. Diehr*, 450 U.S. 175 (1981).
[56] *See* Kevin E. Noonan, *Rapid Litigation Management Ltd. v. Cellzdirect, Inc.* (Fed. Cir. 2016), PATENT DOCS (July 6, 2016), http://www.patentdocs.org/2016/07/rapid-litigation-management-ltd-v-cellzdirect-inc-fed-cir-2016.html.
[57] *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 68, 91 (2012).
[58] *Id*. at 66.
[59] *Id*.

conventional."[60] Further, it is not enough to inform a relevant audience about certain laws of nature, and add steps that "consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately" according to the Court.[61] Many courts have followed this reasoning to invalidate claims to medical diagnostic methods.[62]

In addition to the courts, the U.S. Patent and Trademark Office has adapted its practices for determining patent eligibility to be compliant with the Court's instructions. This has resulted in a two-step approach (Figure 1)[63], as follows:

1. Is the claim is directed to a "natural law" that is subject to a § 101 analysis?
2. A) Is the claim directed to a patentable "judicially recognized exception" under *Mayo/Alice*?[64] (step 2A); and if yes, B) does the claim recite "additional elements that amount to significantly more than the judicial exception"?

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[60] *Id*. at 79-80.
[61] *Id*.
[62] Particularly vulnerable have been claims that recite "a method for diagnosing disease X, by detecting the (presence/absence/changed amount) of marker (gene/protein/metabolite) Y." Approximately 70% of all patents challenged under *Mayo*/*Alice* are found invalid, comparison over 11,000 granted claims. The worst districts for patentees (10 or more §101 decisions) have been the Districts of Delaware, California (Northern), California (Central) (>70% invalid), while the best district for patentees has been the Eastern District of Texas (<35% invalid).
[63] *2014 Interim Eligibility Guidance Quick Reference Sheet*, U.S. PATENT & TRADEMARK OFFICE (2014), https://www.uspto.gov/sites/default/files/documents/2014_eligibility_qrs.pdf. The test consists of three steps, designated by the Office as Step 1, Step 2a and Step 2b.
[64] The Court's *Mayo* decision was further explicated, and its reasoning explained, in a decision unrelated to patent eligibility of diagnostic method claims. *See Alice Corp. Pty. v. CLS Bank Int'l.,* 134 S. Ct. 2347, 2354 (2014).

The USPTO then proceeds with examination for patentability, applying the "broadest reasonable interpretation" of the claims after conducting the subject matter eligibility analysis under these rubrics.[65] When applying the test of what satisfies the requirement for what is "significantly more," the Office applies the standard that "the elements of the claim, considered both individually and as an ordered combination, are sufficient to ensure that the claim as a whole amounts to significantly more than the exception itself."[66] As in many USPTO analyses, the claims must be considered as a whole.[67] In practice, the USPTO's implementation of these Supreme Court decisions have severely limited patenting of diagnostic method claims[68] and set back progress in the development of personalized medicine.[69]

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[65] Memorandum from Robert W. Bahr, Deputy Commissioner for Patent Examination Policy, to the Patent Examining Corps., USPTO (May 4, 2016), https://www.uspto.gov/sites/default/files/documents/ieg-may-2016-memo.pdf [hereinafter "Bahr Memo"].

[66] *Id*.; the Guidances for applying this standard include the note that "[i]ndividually-viewed elements may not appear to add significantly more, those additional elements when viewed in combination may amount to significantly more than the exception." *Id.*

[67] *Id*.

[68] *See* Heidi Ledford, *US Personalized-Medicine Industry Takes Hit from Supreme Court*, 536 NATURE 382 (2016). Summary of Intellectual Property Scholars Conference, presenting data that after *Mayo*, USPTO was more than four times more likely to reject personalized medicine claims as ineligible and applicants were only half as likely to overcome the rejections. Statistically, 5.5% of applications were rejected under § 101 rejections in 2011 and the percentage of applications rejected under § 101 had risen to 22.5% in 2015. Before *Mayo*, 70.7% of § 101 rejections were overcome but that percentage had fallen to 29.7% by 2015. Assuming 1,000 claims, this corresponds to 55 claims being rejected, 39 rejections overcome and 16 maintained prior to the *Mayo* decision and 225 claims rejected, 67 overcome, and 158 maintained after the Mayo decision was rendered. This represents an almost ten-fold increase in diagnostic method claims being rejected by USPTO.

[69] Bernard Chao & Amy Mapes, *An Early Look at Mayo's Impact on Personalized Medicine*, 2016 PATENTLY-O PATENT L. J. 10-14 (2016). This report reviewed one of every ten applications in USPTO Art Unit 1634 (methods for measuring or testing processes involving enzymes or microorganisms). Only subject matter eligibility

Recent Guidance from the USPTO advises that detection methods using novel reagents or detection methods are patent eligible, as are novel treatment methods and specific treatment methods using particular administration routes or methods.[70] Somewhat controversially, the Guidance also indicates that methods of detecting a biomarker that does not recite a diagnostic correlate would also be patent eligible, a policy decision seemingly at odds with at least one Federal Circuit opinion.[71] Patent ineligible methods according to the USPTO's interpretation of the Supreme Court's *Mayo*/*Alice* formula are diagnostic treatment methods broadly reciting a natural law (defined as the correlation between a marker and disease); claims that recite mental steps of drawing the inference regarding the outcome of a diagnostic method and the diagnosis; or claims reciting a higher level of generality between the biomarker and a diagnosis.[72]

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rejections were considered, and their results showed that of the 294 applications considered, 170 (58%) were abandoned, 53 patented, 3 allowed, and 2 on appeal (only 1 of which involved a §101 rejection). Since the time of the study, 196 (67%) have been abandoned, 64 granted, 1 allowed and 1 on appeal (the Examiner having been affirmed in the prior appeal). A random spot check of the newly abandoned and patented claims revealed that no continuing applications were filed in the abandoned applications and narrow claims (*e.g.*, requiring very specific reagents or a treatment step) were allowed in the grated patents.

[70] *See* Bahr Memo, *supra* note 65; *see also Subject Matter Eligibility Examples: Life Sciences*, USPTO (May 2016), https://www.uspto.gov/sites/default/files/documents/ieg-may-2016-ex.pdf.

[71] *See Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015), *cert. denied*, 136 S. Ct. 2511 (2016).

[72] Such claims are exemplified by claims invalidated by the district court, and affirmed by the Federal Circuit. For example, claim 1 of U.S. Patent No. 5,709,999:

> A method for detecting a germline alteration in a BRCA1 gene, said alteration selected from the group consisting of the alterations set forth in Tables 12A, 14, 18 or 19 in a human which comprises analyzing a sequence of a BRCA1 gene or BRCA1 RNA from a human sample or analyzing a sequence of BRCA1 cDNA made from mRNA from said human sample with the proviso that said germline alteration is not a deletion of 4 nucleotides corresponding to base numbers 4184-4187 of SEQ ID NO:1

Related to the Court's views on medical diagnostic claims, the Justices have also rendered decisions on the patent eligibility of natural products.[73] There have been few court cases on this aspect; however, in addition to *UURF v. Ambry Genetics*,[74] the Federal Circuit invalidated claims to chimeric sheep in *In re Rosyln*[75] but declared patent-eligible claims for producing *in vitro* hepatocyte cultures.[76] These decisions are relevant to patenting biomarkers,[77] the prospects for which (at least with regard to unaltered embodiments thereof) have dimmed in the aftermath of the Supreme Court's *Myriad* decision. This is because, by their nature, many of the relevant, diagnostically informative biomarkers are

Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office, 702 F. Supp. 2d 181, 192–211 (S.D.N.Y. 2010).

[73] *Ass'n for Molecular Pathology,* 569 U.S. at 576; Surprisingly, the Court had not directly spoken on the question of subject matter eligibility for natural products until its *Myriad* decision.

[74] *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 755; in this aspect of the decision the Federal Circuit invalidated claims to primer pairs for in vitro amplifying portions of the human BRCA genes informative for genetic diagnostics predicting the likelihood of developing breast or ovarian cancer.

[75] *In re Roslyn Inst. (Edinburgh)*, 750 F.3d 1333 (Fed. Cir. 2015); the appellate court's decision relied on the fact that the claimed sheep were, indeed, sheep (albeit genetically identical to the sheep from which they were produced by *in vitro* nuclear transfer to enucleated eggs). It is undetermined whether other ways to distinguish the claimed product would be patent eligible (for example, a claim to a genetically identical *flock* of sheep).

[76] *Rapid Litig. Mgmt. Ltd. v. Cellzdirect, Inc.*, 827 F.3d 1042 (Fed. Cir. 2016); a non-trivial distinction between the claims at issue in this case and diagnostic method claims invalidated in other decisions is that these claims have a tangible outcome (the *in vitro* hepatocyte cultures produced by the claimed methods) as opposed to intangible diagnostic information produced by conventional medical diagnostic claims.

[77] Examples of these molecules include those that are nucleic acid-based (*e.g.*, single nucleotides polymorphisms or SNPs, and chromosomal rearrangements); protein-based (*e.g.*, sickle cell anemia); immunological (antigens, antibodies, cytokines); metabolites (endogenous or produced in response to drugs, diet, etc.); and more complex phenotypes. *See* Alkes L. Price et al., *Progress and promise in understanding the genetic basis of common diseases*, 282 PROC. R. SOC. B 20151684.

natural products,[78] and the reasoning behind the Court's *Myriad* decision suggests that mere isolation is not enough to confer patent eligibility to such molecules.[79] What may be needed (suggested by the Myriad decision) is that whatever is claimed has somehow been changed from how it exists in nature;[80] the safest course may be by a structural change to the biomarker, most typically by being conjugated or otherwise labeled with a detectable marker.[81]

In the USPTO, recent Guidance[82] has set forth examples of what is considered

[78] While no court has rendered a decision affirming this characterization, the language of the Court's *Myriad* opinion suggests that conventionally patent eligible molecules (antibiotic, antibodies, vitamins, vaccines, etc.) may not remain patent eligible.

[79] The Court's *Myriad* decision held that genomic DNA (or indeed any DNA molecule that had the structure found in a human chromosome) was patent ineligible because it had not been sufficiently changed from how it occurred in nature to evidence the "hand of man" as set forth in the Court's *Chakrabarty* decision. *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980). Complementary DNA (cDNA), produced by reverse transcription of messenger RNA could be eligible under the Court's decision, provided it showed such differences; in higher organisms like man, *for example*, most cDNAs differ from the corresponding genomic DNA progenitors because so-called intervening DNA (or introns) have been spliced out during mRNA maturation. It is clear that the Court recognized the need for human intervention to produce cDNA from mRNA; it is less clear that the Court appreciated that removing intron sequences (a process known as splicing; Dean H. Hamer & Philip Leder, *Splicing and the formation of stable RNA*, 18 CELL 1299, 1299-1302 (1979)) was naturally performed inside the cell. *Ass'n for Molecular Pathology*, 113 S. Ct. at 2109.

[80] Purification or increased concentration or potency may not be enough, however. *Id.*

[81] While such distinctions have formed the basis for USPTO policy on natural products patenting, it must be recognized that many structural alteration have the capacity or likelihood to alter relevant biological activity (binding specificity or affinity, biological half-life, antigenicity, etc.). *Id.*

[82] Earlier iterations of such Guidances were criticized for being overly exclusive of patent eligibility. For example, gunpowder was deemed ineligible has being merely a mixture of elemental sulfur, charcoal and saltpeter (KNO_3), until it was pointed out that the mixture (but not combination of its components) had the capacity to explode. In addition, review of 1355 drugs approved by the FDA from 1980-2010 indicated that the majority of anticancer drugs (80%) and antibiotic drugs (75%) would be patent ineligible under the earlier standards promulgated by the USPTO in response to the Supreme Court's *Mayo* and *Myriad* decisions. *See* David J. Newman & Gordon M. Cragg, *Natural*

patent eligible and what is not for both diagnostic method claims and natural products.[83] For "products of nature," these include: products comprising alterations (*e.g.*, mutations, chemical reactions, changes in structure or physical form) not found in nature; formulations (particularly with components not found together in nature) that change properties or functional characteristics of product of nature; and nonconventionality of other aspects of the claimed invention (microneedles used for vaccination being exemplified in the Guidance).[84] On the other hand, products of nature per se (*i.e.*, having no differences except concentration or specific activity from their presence in nature);[85] and combination of product of nature with other substances that do not change physical properties or other characteristics.[86] Nevertheless, diagnostic reagents per se are likely to be ineligible, and according to the Court's *Myriad* decision merely producing a reagent synthetically will not render claims to the reagent patent eligible provided that the structure is the same as exists

Products as Sources of New Drugs over the 30 Years from 1981 to 2010, 75 J. NAT. PROD. 311, 311-35 (2012). 81 Fed. Reg. 27381 (May 6, 2016).

[83] May 2016 Subject Matter Eligibility Update, 81 Fed. Reg. 27381 (May 6, 2016), https://www.gpo.gov/fdsys/pkg/FR-2016-05-06/pdf/2016-10724.pdf [hereinafter "May 2016 Subject Matter Eligibility Update"]. *See* Kevin E. Noonan, *USPTO Releases Memorandum on Subject Matter Eligibility*, PATENT DOCS (July 18, 2016), http://www.patentdocs.org/2016/07/uspto-releases-memorandum-on-subject-matter-eligibility.html#comments; *see also* Kevin E. Noonan, K., *The Recent PTO Guidance on Subject Matter Eligibility: Lessons*, PATENT DOCS (May 25, 2016), http://www.patentdocs.org/2016/05/the-recent-pto-guidance-on-subject-matter-eligibility-lessons.html

[84] *See supra* note 83.

[85] It is unclear whether a specific preparation at a therapeutically useful concentration would be patent eligible without more; it may be presumed that a pharmaceutical composition comprising excipients or other components would be considered a specific subset of patent-eligible formulations but there is no decision affirming this expectation.

[86] This reasoning relies expressly and heavily on the Supreme Court's 1948 *Funk Brothers Seed Co. v. Kalo Inoculant Co.* decision (333 U.S. 127 (1948)), expressly reaffirmed in the Court's *Myriad* decision after more than a generation of being ignored.

in nature.[87]

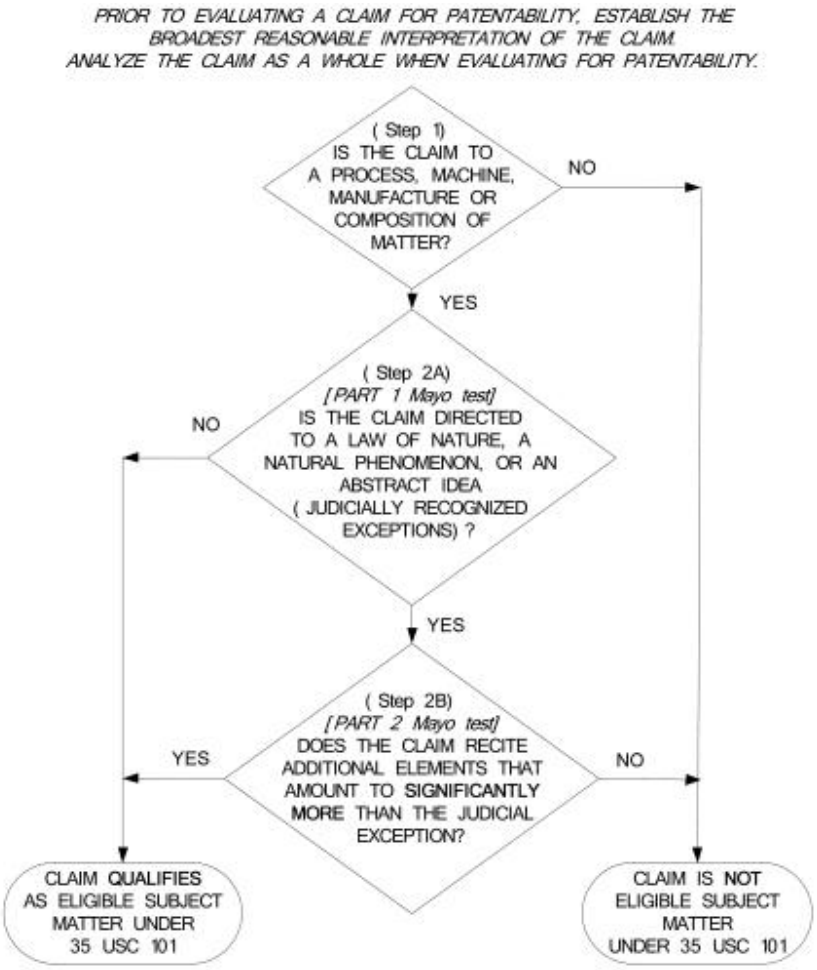
7. Conclusion

Despite these challenges, it is uncontested that the application of technology to medical practice will continue (albeit its pace will likely be affected by whether such technologies can be protected, by patent, trade secret protection or otherwise). With increased vulnerability of seemingly any information stored in electronic form, increased diligence in protecting patient information will need to be adopted if the legal and societal responsibilities of record keepers are to be satisfied.

[87] *Ass'n for Molecular Pathology*, 113 S. Ct. at 2109.

Figure 1

U.S. Patent and Trademark Office test for determining patent eligibility consists of three steps, designated by the Office as Step 1, Step 2a and Step 2b.[88]



[88] *2014 Interim Eligibility Guidance Quick Reference Sheet*, U.S. PATENT & TRADEMARK OFFICE (2014), https://www.uspto.gov/sites/default/files/documents/2014_eligibility_qrs.pdf.