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Patents and Genome-Wide DNA Sequence Analysis: Is it Safe to go into the Human Genome?

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Introduction

Whether, and to what degree, do patents granted on human genes cast a shadow of uncertainty over genomics and its applications? Will owners of patents on individual genes or clusters of genes sue those performing whole-genome analyses on human samples for patent infringement? These are related questions that have haunted molecular diagnostics companies and services, coloring scientific, clinical, and business decisions. Can the profusion of whole-genome analysis methods proceed without fear of patent infringement liability?

Whole-genome sequencing (WGS) is proceeding apace. Academic centers have been performing whole-genome and -exome sequencing (WES) as research for at least five years, and academic clinical laboratories with national reach have been doing sequencing for clinical applications for almost as long. Companies have also been offering WGS and WES as a clinical service for a few years now. So far as we know, no one has been sued for infringement of “gene patents” by performing WGS.

Patents on Gene Sequences and Methods of Genetic Diagnosis

“Gene patent” is a fuzzy term applied to patents based on the discovery of individual genes, and roughly corresponds to a subset of 15,359 US patents that make claims to a DNA sequence.[1] The exact number of “gene patents” that map to the human genome also remains uncertain with empirical studies using different methods, each with their own limitations, and yielding differing results.[2] Only a small fraction of those human “gene patents,” have claims that could arguably be infringed by whole-genome analysis. And of those claims that might be infringed, a sizeable fraction would not be valid and enforceable in the wake of recent US court decisions.

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Legal scholars have noted that the problem of pervasive infringement risk is overstated, and that WGS is unlikely to be seriously impeded by patent rights.[3] Some patent claims, exemplified in Table 1, might appear on their face to be infringed by whole-genome analysis, because they would use methods that reveal mutations in patented genes (diagnostic method claims) or they would entail making DNA molecules described in patent claims on individual genes (DNA composition of matter claims).

As a practical matter, however, it is unlikely that anyone doing WGS will be sued for infringement of patents that were granted on individual genes. This is particularly true for noncommercial academic research, but infringement liability risk is probably also low even for commercial WES or WGS. This conclusion is possible despite considerable angst and uncertainty about how patents will be interpreted, and shifting jurisprudence in federal courts.

Practical Reasons Mitigating Infringement Liability

The reasons for being sanguine about risk of infringement liability of patents (although not necessarily all patents, just those on genes and methods of characterizing them such as identifying gene mutations) are both legal and pragmatic. The main pragmatic reason is that most uses of whole genome analysis are not worth suing over, at least for now. Most WGS uses are still in research settings, and except for patented research tools, the damages that would be expected from a patent infringement suit would not justify the expenses. Suing researchers, while clearly within the law, is not likely to accomplish much good for the patent-holder unless researchers are the main consumers of the patented product or service. Even if a patent-holder prevailed, the damages would be small since research generally does not take away from commercial revenues, unless the patents cover tools sold into a research market. And WGS is not a research tool, *per se*, but rather a process that creates information interpreted as part of the research process. Moreover, suing researchers would be unpopular, and unlikely to find favor with a judge and/or jury during litigation. Does a company really want to sue those doing research on breast cancer? And most uses of WGS are likely to add value, rather than cause damage, to the patent-holder's estate, by potentially discovering new utilities of patented genes.

WGS is unlikely to become a direct competitor with a single or multi-gene genetic test, although that picture could change in coming years. If costs and reliability of WGS come into the range of current genetic tests, then WGS could supplant them and recent developments suggest this is possible. More to the point, however, a gene-patent holder might well lose in any effort to enforce gene patent rights over those doing WGS. It was far from clear even before recent cases, that claims on a single-gene would successfully impede WGS, especially when using next generation sequencing technologies. Prospects of a gene patent-holder prevailing in such a case further dimmed after Supreme Court decisions in 2012 and 2013 which are discussed in greater detail below. Patent lawsuits generally cost millions to tens of millions of dollars, and a patent-holder must generally be sure of victory or truly at risk in order to initiate such a suit. While WGS might eventually supplant much or all of genetic testing for individual conditions, most first-generation gene patents—the patents most likely to contain broad claims—will be expiring in the next several years.

Winning a patent suit would thus forestall competition only briefly. In summary, several practical considerations will dissuade a gene patent-holder from suing someone engaged in WGS.

This conclusion is subject to several caveats, however. Feldman and Price have sounded an alarm about the risk of private firms whose business model is to aggregate patent rights and extract revenues under threat of litigation, and an emerging threat specifically in biotechnology and pharmaceuticals.[4] "Patent trolls" have emerged in cell phones, information technology, and Internet business methods. Patent assertion entities have not generally been perceived as a major problem in biotech or the life sciences, but Feldman and Price are concerned that they could. One foreseeable scenario would be collecting patents on genes—including university-based patents—and threatening to assert them, because the claims in some such patents are broad, and the risk of litigation may be high enough to justify settling quickly out of court. The factors that Feldman and Price note are credible, but for the practical reasons noted above and the legal reasons that follow, lawsuits over individual gene patents seem unlikely to prove a serious impediment to WGS. But unlikely does not mean impossible. Only time will tell if asserting patents against molecular diagnostics emerges as an issue.

Legal Constraints on Infringement Liability

The legal basis for assessing infringement liability is far more complex than the practical rationale, because patents that have been granted contain claims that do appear on surface to be infringed by WGS (see Table 1). However merely identifying patents, and reading their granted claims cannot accurately assess infringement liability. Many such claims would be considered invalid in the wake of recent court decisions, as we note below. The extent of patent infringement liability risk is simply not clear.

One obvious exception to this "litigation unlikely" assessment is the ongoing litigation over patents covering *BRCA1*, *BRCA2* and *MUTYH* brought against commercial laboratories that entered the market soon after the Supreme Court decision in *Association of Molecular Pathology v Myriad Genetics* (hereafter, *Myriad*) on June 13, 2013.[5] This ongoing litigation, however, is an unusual outlier case and unlikely to be repeated. The litigation was a strategic response by Myriad Genetics to the Supreme Court decision in defense of Myriad's business model, a model that is highly unusual. The *BRCA* testing market is large and lucrative, *BRCA* testing constituted a large majority of Myriad's revenue stream, and Myriad has stockholders who might sue Myriad's management if Myriad did not mount a vigorous, even if ultimately fruitless, defense of the patent estate underlying its flagship product. Even here, the litigation is focused on genetic testing for a handful of genes, not over WGS per say. Indeed in the one case settled out of court, among ten suits and counter-suits that are being consolidated, Gene by Gene agreed not to do *BRCA1/2* testing in the United States, but did *not* agree to cease WGS services.[6] Myriad thus appears unlikely to enforce its patents against WGS, and yet Myriad is among the few potential litigants that might have motivations to do so. While is difficult to foresee all situations in which lawsuits might arise, the facts that WGS was addressed in the Myriad case during appeal and that an out-of-court settlement permitted WGS both point toward low infringement liability risk for WGS.

Does WGS Infringe Patents on Individual Genes?

The assessment of low infringement liability risk must be tempered by caveats about legal uncertainty. Strict legal interpretation of infringement liability is always uncertain, and all the more so in an area where court decisions are changing the rules. The legal landscape can be described only by a trek through the arcana of patent law and the history of recent cases detailed below.

On April 4, 2012, Judge William Bryson of the Court of Appeals for the Federal Circuit asked the question that is central to the future of genome-wide sequence analysis: *would patents on the BRCA1 and BRCA2 genes be infringed by sequencing and analyzing an individual's entire genome*?[7] Table 1 contains some representative claims from patents-in-suit in the *Myriad* case. If one reads those claims as plain English, the answer to Judge Bryson's question would be "yes," the claims are infringed. Any method that noted a difference in sequence between a DNA sample sequence and Myriad's reference *BRCA1* sequence would infringe the broad method claims ('001 and '441 patents), for example. It would not matter that the sequencing was performed on the entire genome if the "isolated" DNA in the claim refers to DNA "in a test tube," not necessarily DNA specific to *BRCA1* and *BRCA2* culled away from or selectively amplified over other DNA (see below). But as a legal matter, and by interpreting the language of patent claims in light of the patent specification, the answer might be "no, these claims are not infringed."

The colloquy that followed Judge Bryson's question was confused and ultimately incoherent and inconclusive.[8] Myriad's lawyer, Gregory Castanias, first ventured that because the DNA of whole-genome analysis did not first "isolate" *BRCA1* or *BRCA2* genes away from other genes, whole genome analysis would not infringe. On further reflection, however, Mr. Castanias had "not conferred with his clients" about whether whole-genome analysis would constitute infringement. Several minutes later, Christopher Hansen, the lawyer representing the American Civil Liberties Union, argued that the patents *would* be infringed by WGS. In Hansen's view, that problem illustrated how broad the patents were, and a reason to render them invalid.[9]

Judge Bryson specifically worried whether anyone analyzing an individual's entire genome might need licenses from hundreds of patent-holders for individual genes. This very prospect kept some scientists up at night, a quagmire of patents on individual genes that would have to be licensed before studying complex biological phenomena that involve DNA sequencing; an even more daunting problem if developing a clinical genomic profile, such as a commercial genomic test that might involve sequencing dozens or hundreds of cancer genes or cardiovascular risk genes. This was the prospect of an "anticommons" that Heller and Eisenberg posited in 1998.[10] The difficulty of aggregating sufficient atomized intellectual property might thwart progress in science and medicine. Indeed, disputes over the extent of "gene patenting"[11] and its possible untoward effects on research and development of diagnostics have a long and contentious history.[12]

Contradictory answers from opposing lawyers are no surprise, but this question is central to science. How can there be such uncertainty about such an important question? It turns on a

long-standing doctrine of patent law, that one cannot claim something found in nature or an abstract idea, but an invention (or discovery) can be patented if it is put into tangible and useful form that requires human ingenuity. In these patent claims, the ambiguity traces to a single word; the term “isolated” in the patent claims.

What Does “Isolated” Mean?

The meaning of “isolated” in Myriad’s (and many other) patent claims is unclear. “Isolated” is used in several different senses in the patent itself, and the explicit definition used in the patent is hopelessly vague. In some contexts, isolated means extracting DNA in solution, in others, separating DNA from other cellular components and debris, in others selectively amplifying target DNA so it’s abundance far exceeds other DNA sequences that are thereby rendered undetected. The ambiguity of “isolated” cannot be resolved by reading the patent. If “isolated” means “we claim any DNA molecule we describe in our claims if it is in a lab or test tube, not naturally residing in the body”—the “artificial state of affairs” as a trial court judge, Justice Nicholas in Australia, interpreted similar claims to mean[13]—then the claims would be infringed. This conclusion would follow from answering two other questions: (1) “Is the DNA molecule isolated in an artificial setting (e.g., a DNA sequencing instrument) when its sequence is being determined?” And (2) “Is it eligible to be patented if that DNA molecule has the same sequence as the sample DNA sequence from which it was copied?” If the answer to both questions is “yes,” then anyone who analyzes the genome will of course create DNA molecules of greater than 15 base pairs containing *BRCA* sequences, infringing claims 5 and 6 of US Patent 5,747,282 (see Table 1). Whole genome sequencing would also necessarily entail generating DNA molecules with *BRCA* sequences; if the DNA were not isolated from its natural setting, its sequence could not be read. In this sense, “isolated” is a very broad term that signals some human intervention, and under that broad meaning, such claims would be infringed by WGS.

If, however, “isolated” means “we claim only DNA molecules containing *BRCA* sequences that have been teased away from other DNA in that genome,” then claims might be narrow enough that whole-genome sequence analysis would not infringe, depending on the steps followed in making the DNA molecules for analysis and detecting mutations. That is, if the claims required an “isolation” step separating *BRCA1* and *BRCA2* DNA from other DNA *within* the genome, then most forms of WGS would not entail infringement.

The way DNA is generally prepared for genetic testing, including in Myriad’s own laboratory, is to amplify only those segments of DNA lying between PCR primers selected to span coding sequences, so that the only DNA in sufficient quantity to sequence, comes from those segments of DNA that have been amplified. That DNA is not “isolated” in the way any scientist would normally use the term. It is amplified, extracted and sequenced in around 82 PCR amplicons containing sequences spanning *BRCA1* and *BRCA2* coding domains on chromsomes 17 and 13. But it is not “snipped” out of the genome or “isolated” from other DNA at any particular step. The DNA segments are amplified to the degree that other DNA fades into the background as they become less abundant. “Isolated” is an odd term to use for such a process. Why, then, was that the word used in the patent claims? The simplest answer is that it became a term of art that was intended to confer patent-eligibility,

signaling that the DNA had been touched by the hand of man. Without such a term, the claims would surely fail the "product of nature" doctrine constructed in a series of Supreme Court cases (most of which predate the 1952 revision of the Patent Act, which deliberately reduced reliance on the significance of the distinction between discovery and invention). That is, without "isolated" in the claims, DNA corresponding to naturally occurring sequences would not be eligible to patent. No one could claim the DNA in your body, and "isolated" is the word that was chosen to signal human intervention. The problem is that there has been scant case law to determine what it means until recent patent lawsuits described below, that raise the issue of what can be patented into stark relief.

Mayo v Prometheus

The tectonic shift in diagnostic method jurisprudence, arguably more important than *Myriad*, results from *Mayo v Prometheus.*[14] This decision has implications for genetic diagnostic methods, and it is method claims that would most often be infringed by diagnostic genetic testing.[15] This case concerned a patent on measuring a metabolite of thiopurine drugs and adjusting doses upward or downward accordingly. Mayo Medical Laboratories (Mayo) had initially licensed the patent from Prometheus, but then changed its laboratory routines and dosing regimens, and ceased licensing. Prometheus sued Mayo in return.

Mayo's laboratory has a national reach and conducts genetic testing for health systems well beyond The Mayo Clinic itself. It has a very systematic committee-based process for making in-licensing and out-licensing decisions about patents. Mayo has many patents, and licenses many others; this patent from Prometheus, however, the Mayo committees could not abide. The Court of Appeals for the Federal Circuit upheld the Prometheus patents twice, one of them after being heard by the entire court *en banc* (most patent appeals cases are heard in panels of three judges). Mayo decided to appeal as far as it could, and that led to two visits to the Supreme Court. The Supreme Court, eventually, reversed the CAFC and unanimously invalidated the Prometheus patent.[16] This signaled that diagnostic method claims in granted patents might be invalid, and clearly reversed the CAFC affirmations of such claims in Prometheus patents.

AMP vs. Myriad

The *Myriad* case[17] is by far the most conspicuous gene patent lawsuit. It began in May 2009, lagging behind *Mayo v Prometheus* by one year. The American Civil Liberties Union and Public Patent Foundation brought it against Myriad Genetics on behalf of twenty plaintiffs. Some plaintiffs were women who wanted testing but had encountered one obstacle or another. Some were Medicaid patients in states that had not negotiated payment agreements with Myriad. Some wanted to verify their test results with another laboratory. Some plaintiffs were laboratory directors who wanted to offer testing but where thwarted by patent infringement liability. Other plaintiffs were professional associations of laboratory physicians, of medical geneticists, and organizations of women's health advocates, and breast cancer activists. The plaintiffs sued Myriad, the University of Utah trust that holds patents developed at the university, and the US Patent and Trademark Office.

In March 2010, Judge Robert Sweet, from the federal District Court for Southern New York handed down his summary judgment that invalidated all fifteen claims challenged in seven patents whose rights were controlled by Myriad Genetics.[18] This was a shock to many in patent law. Judge Sweet's 156-page ruling was assisted by his clerk, Herman Yue, who had a PhD in molecular biology from UC Berkeley. In his ruling, Judge Sweet revisited the case law on which "product of nature" and "law of nature" was described. His ruling was clearly written for the higher courts, destined for appeal.

The Myriad case, like *Mayo v Prometheus* before it, was heard twice by the Court of Appeals. Oral arguments in April 2011 led to an October 2011 ruling that upheld Judge Sweet's invalidation of five method claims (including several in Table 1) and also allowed standing to just one of the twenty plaintiffs, Harry Ostrer, who had been sent a cease and desist letter by Myriad and had also pledged to start *BRCA* testing should the patents be invalidated. The Court of Appeals also upheld one method claim on a drug-discovery assay.[19] The invalidation of broad method claims, the affirmation of one method claim on use of BRCA in drug discovery assays, and the decision on standing of Harry Ostrer were unanimous among the three judges: Lourie, Moore, and Bryson.

The trio split 2-1, however, when it came to the claims on BRCA1 DNA molecules. Judges Lourie and Moore upheld the composition of matter claims on isolated DNA, although for somewhat different reasons (Judge Lourie, stated it was a molecule different from one found in nature because covalent bonds were broken; Judge Moore relied on a combination of structural difference and utility that would not pertain to naturally occurring DNA). Judge Bryson dissented and argued the claims on isolated DNA molecules were invalid.

The case was appealed to the Supreme Court, which then remanded the case back to the Court of Appeals in light of its 2012 ruling in *Mayo v Prometheus* (see above). The Court of Appeals reiterated its judgment that the DNA molecule claims in Myriad's patents were patent-eligible, and argued that the *Mayo* decision was not about molecules but methods and thus not directly relevant. CAFC changed very little from its 2011 ruling that upheld Myriad's DNA molecule claims as patent-eligible. In November, 2012, the Supreme Court again agreed to hear *Myriad* on appeal (granted "writ of certiorari").[20] *The* Supreme Court heard oral arguments on April 15, 2013, and handed down its ruling on June 13, 2013. The Supreme Court unanimously ruled that "A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring."[21]

Invalidity of Methods Claims for Comparing Sequences of Individual Genes

Anyone who sequenced an entire genome and compared the sample's *BRCA* sequences to the wild type reference sequence and detecting differences would arguably infringe method claims from US patents such as those shown in Table 1. In sequencing the genome they would include *BRCA1* and *BRCA2*, and they would note alternations in those genes' sequences. A laboratory doing WGS and following the recent recommendations of the American College of Medical Genetics (ACMG),[22] for example, would infringe such claims because *BRCA1* and *BRCA2* were both among the genes that should be analyzed for

deleterious, actionable mutations, which, if detected, should be returned to the patient. That is, according to ACMG, any clinical use of WGS should entail deliberately looking for sequence variations in *BRCA1* and *BRCA2*. Since the patent claims read on any method of comparing sample sequence to reference sequence and detecting "alterations," this would be infringed by any way of noting such differences, including WGS. However, Judge Sweet invalidated these claims at the district court level and that part of his judgment was affirmed by the CAFC upon appeal. The courts agreed that the five broad method claims based on "comparing" and "detecting" differences in *BRCA* were granted erroneously, and are invalid. [23]

So the simple answer to Judge Bryson's question is that yes, the language in many of the claims was drafted to be broad and capture any way of detecting mutations in particular genes, which would also include research or commercial testing of DNA that includes those genes. But courts have been quite concerned about the breadth of such claims, and have handed down a series of decisions that make many such broad claims invalid. This means that whole-genome analysis methods in research, and even in commerce, are likely to entail low risk of infringement liability from claims on individual gene sequences and methods for detecting differences in individual genes. Broad method claims for detecting mutations in individual genes might have been granted, but they are unlikely to prove valid and enforceable. But again, that risk is not zero. The upshot for those doing whole-genome analysis is that they will labor under some residual uncertainty, although the risks in 2014 are considerably lower than they would have been before 2012.

Post-Supreme Court Litigation

The very day that the Supreme Court handed down its decision in *Myriad*, Gene by Gene and Ambry Laboratories, both started offering competing *BRCA* tests. Several academic genetic testing laboratories also quickly started offering *BRCA* testing. Over the following several weeks, more companies announced their intention to start *BRCA* testing, including one of the most nationally prominent genetic testing laboratories, GeneDx, and the two largest diagnostic commercial laboratory conglomerates, Quest and LabCorp.

On July 9, 2013, Myriad and its co-plaintiffs (University of Pennsylvania, University of Toronto, and Endorecherche of Montreal) filed suit against Ambry [24], and on July 10, against Gene by Gene. The Ambry case was assigned to Judge Robert Shelby in Utah federal district court. Since then, Myriad has sued GeneDx, Quest, Labcorp, and Invitae in Utah federal district court. These cases, along with petitions for declaratory judgment against Myriad in other district courts, have either already been consolidated in the court of Judge Shelby (Ambry, Counsyl, Quest, and GeneDx)[25] or notice of consolidation is in process (Labcorp and Invitae). Their decisions are still awaited.

Simultaneous to filing the patent infringement suit against Ambry, Myriad also requested a preliminary injunction, [26] a judge-ordered ruling that would force Ambry to stop offering *BRCA* testing. On March 10, 2014, US District Court Judge Robert Shelby denied Myriad's motion for an injunction.[28] This is significant for two reasons. First, it permits Ambry to continue offering *BRCA* testing while the case progresses. Myriad is no more likely to

prevail against other competitors, so other laboratories are likely to continue to offer *BRCA* testing also. Second, the decision explicitly indicates Judge Shelby's discomfiture with the validity of Myriad's claims. Subsequent steps in this case will likely take place in his court. He agreed with Myriad that it would suffer irreparable harm by allowing competition to continue; but he also found that Myriad's prospects of prevailing were not certain enough to justify an injunction because of strong arguments against the validity of their patent claims.

The bulk of Judge Shelby's 106-page decision is focused on whether the primer molecules and methods being enforced against Myriad's competitors are eligible to be patented.[27] There are two general classes of claims: one set is on DNA molecules in the form of primers or pairs of primers; the other claims are on methods. Judge Shelby's main concern is that the sequences claimed, including pairs or primers for amplifying DNA correspond to sequences found in naturally occurring DNA. (Many primers actually flank coding sequences, so are not specified in cDNA sequences, but they are nonetheless found in the expanse of chromosomal DNA corresponding to the *BRCA1* and *BRCA2* genes before removal of exons in making a cDNA copy.) And Judge Shelby argues that Myriad's method claims are invalid for the same reasons that the broader method claims were struck down in the previous *Myriad* case and in *Mayo v Prometheus.* On March 13, Myriad appealed the denial of their motion for an injunction to the Court of Appeals.[28]

Conclusion

What do the recent cases tell us about the shadow of infringement liability hanging over WGS? Even before the *Myriad* case, some patent scholars believed the risk of infringement liability for many forms of WGS was low; after the succession of decisions adverse to holders of patents relevant to diagnostics, that argument is even stronger. The prospect of those performing WGS needing to license hundreds, or thousands of patents on individual genes, seems unlikely. Given the nature of the claims that had been granted on DNA molecules and on DNA methods by the USPTO, infringement liability was a real prospect before recent court decisions; but Supreme Court decisions have decisively altered the landscape. There may well be patent battles, but they are unlikely to arise from patents on individual genes.

In summary, the vast majority of valid claims on DNA molecules and methods would not be infringed by WGS. Many claims that have been granted and might be infringed by WGS are vulnerable to challenge on grounds of patentable subject matter, utility, novelty, obviousness, enablement, or written description. If the claims are so broad that they apply to WGS based on having characterized a single gene, they are apt to be vulnerable to challenge. This renders the likelihood of those holding patents on individual genes prevailing in a suit against WGS low, opening up freedom to practice WGS for clinical and research uses.

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Biographies

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Box 1

Representative claims from US patents that could be interpreted as infringed by WGS

Claims on DNA moleculesld

US Patent 5,747,282 (*BRCA1*, inherited risk of breast, ovarian and other cancers)

1 An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2 (brca1 peptide).

2 The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1 (*BRCA1* cDNA).

5 An isolated DNA having at least 15 nucleotides of the DNA of claim 1.

6 An isolated DNA having at least 15 nucleotides of the DNA of claim 2.

16 A pair of single-stranded DNA primers for determination of a nuycleotide [sic] sequence of a BRCA1 gene by a polymerase chin [sic] reaction, the sequence of said primers being derived from human chromosomne [sic] 17q, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence of the *BRCA1* gene.

US Patent 5,679,635 (*ASPA*, Canavan disease)

1 An isolated nucleic acid molecule comprising: (a) a nucleic acid sequence encoding a human aspartoacylase polypeptide; (b) a nucleic acid sequence fully complementary to nucleic acid sequence (a); or (c) a nucleic acid sequence at least 16 nucleotides in length capable of hybridizing specifically with one of said nucleic acid molecules (a) or (b).

Claims on methods

US Patent 5,753,441 (*BRCA1,* inherited risk of breast and ovarian cancer)

1 A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject.

US Patent 5,710,001 (*BRCA1*)

1 A method for screening a tumor sample from a human subject for a somatic alteration in a BRCA1 gene in said tumor which comprises gene comparing a first sequence selected form the group consisting of a BRCA1 gene from said tumor sample, BRCA1 RNA from said tumor sample and BRCA1 cDNA made from mRNA from said tumor sample with a second sequence selected

from the group consisting of BRCA1 gene from a nontumor sample of said subject, BRCA1 RNA from said nontumor sample and BRCA1 cDNA made from mRNA from said nontumor sample, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said tumor sample from the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said nontumor sample indicates a somatic alteration in the BRCA1 gene in said tumor sample.

US Patent 5,709,999 (BRCA1)

1 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.

US Patent 5,750,400 (BRCA1, amplifying and sequencing method for detecting variants)

5 A method of detecting an increased genetic susceptibility to breast and ovarian cancer in an individual resulting from the presence of a mutation in theBRCA1 coding sequence, comprising:

a. amplifying a DNA fragment of an individual's BRCA1 coding sequence using an oligonucleotide primer which specifically hybridizes to sequences within the gene;

b. sequencing said amplified DNA fragment by dideoxy sequencing;

c. repeating steps (a) and (b) until said individual's BRCA1 coding sequence is completely sequenced;

d. comparing the sequence of said amplified DNA fragment to aBRCA1.sup.(omi) DNA sequence selected from the group consisting of: SEQ ID NO: 1 together with SEQ ID NO: 3, SEQ ID NO: 1 together with SEQ ID NO: 5, SEQ ID NO: 3 together with SEQ ID NO: 5, SEQ ID NO: 1 together with SEQ ID NO: 3 together with SEQ ID NO: 5, SEQ ID NO: 3 and SEQ ID NO: 5;

e. determining any sequence differences between said individual's BRCA1coding sequences and a BRCA1.sup.(omi) DNA sequence selected from the group consisting of: SEQ. ID. NO.: 1 together with SEQ ID NO: 3, SEQ ID NO: 1 together with SEQ ID NO: 5, SEQ ID NO: 3 together with SEQ ID NO: 5, SEQ ID NO: 1 together with SEQ ID NO: 3 together with SEQ ID NO: 5, SEQ ID NO: 3 and SEQ ID NO: 5 in order to determine the presence or absence of base changes in said individual's BRCA1 coding sequence wherein a base change which is not any one of the following:

i. C and T at position 2201,

ii. T and C at position 2430,

iii. C and T at position 2731,

iv. A and G at position 3232,

v. A and G at position 3667,

vi. T and C at position 4427, and

vii. A and G at position 4956, is correlated with the potential of increased genetic susceptibility to breast or ovarian cancer resulting from a BRCA1 mutation in the BRCA1 coding sequence.

US Patent 7,993,835 (BRCA2, specific mutations conferring risk of breast, ovarian and other cancers)

1 A method for detecting a mutation in a BRCA2 allele comprising: analyzing a BRCA2 nucleic acid from a sample obtained from a human subject; and detecting a mutation in said nucleic acid wherein said mutation results in the deletion of five nucleotides beginning at position 4,633 of a BRCA2 cDNA.

US Patent 5,508,167 (*ApoE*, Alzheimer's disease)

1 A method of detecting if a subject is at increased risk of developing late onset Alzheimer's disease (AD) comprising directly or indirectly: detecting the presence or absence of an apolipoprotein E type 4 isoform (ApoE4) in the subject; and observing whether or not the subject is at increased risk of developing late onset AD by observing if the presence of ApoE4 is or is not detected, wherein the presence of ApoE4 indicates said subject is at increased risk of developing late onset AD.

US Patent 7214483 (KCNQ2 and KCNQ3, potassium channel genes mutated in benign familial neonatal convulsions (BFNC) and other epilepsies)

1 A method for diagnosing the presence of a mutation in human KCNQ2 which causes BFNC or rolandic epilepsy wherein said method is performed by means which identify the presence of said mutation, [lists specific mutations].

2 The method of claim 1 wherein said means comprises sequencing human KCNQ2.

Table 1

Representative claims from US patents that could be interpreted as infringed by WGS

Type of claim	US Patent Number/Title (use)	Representative Claims
DNA Composition of Matter	US 5,747,282 17Q-linked breast and ovarian cancer susceptibility gene *(BRCA1,* inherited risk of breast, ovarian and other cancers)	Claim 1: An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2 (brca1 peptide). Claim 2: The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1 (*BRCA1* cDNA). Claim 5: An isolated DNA having at least 15 nucleotides of the DNA of claim 1. Claim 6: An isolated DNA having at least 15 nucleotides of the DNA of claim 2. Claim 16: A pair of single-stranded DNA primers for determination of a nuycleotide [sic] sequence of a BRCA1 gene by a polymerase chin [sic] reaction, the sequence of said primers being derived from human chromosomne [sic] 17q, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence of the *BRCA1* gene.
	US 5,679,635 Aspartoacylase gene, protein, and methods of screening for mutations associated with Canavan disease (ASPA gene)	Claim 1: An isolated nucleic acid molecule comprising: (a) a nucleic acid sequence encoding a human aspartoacylase polypeptide; (b) a nucleic acid sequence fully complementary to nucleic acid sequence (a); or (c) a nucleic acid sequence at least 16 nucleotides in length capable of hybridizing specifically with one of said nucleic acid molecules (a) or (b).
DNA Diagnostic Method	US 5,753,441 170-linked (sic) breast and ovarian cancer susceptibility gene *(BRCA1,* inherited risk of breast and ovarian cancer)	Claim 1: A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject.
	US 5,710,001 17q-linked breast and ovarian cancer susceptibility gene *(BRCA1,* inherited risk of breast and ovarian cancer)	Claim 1: A method for screening a tumor sample from a human subject for a somatic alteration in a BRCA1 gene in said tumor which comprises gene comparing a first sequence selected form the group consisting of a BRCA1 gene from said tumor sample, BRCA1 RNA from said tumor sample and BRCA1 cDNA made from mRNA from said tumor sample with a second sequence selected from the group consisting of BRCA1 gene from a nontumor sample of said subject, BRCA1 RNA from said nontumor sample and BRCA1 cDNA made from mRNA from said nontumor sample, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said tumor sample from the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said nontumor sample indicates a somatic alteration in the BRCA1 gene in said tumor sample.
	US 5,709,999 Linked breast and ovarian cancer susceptibility gene *(BRCA1,* inherited risk of breast and ovarian cancer)	Claim 1: 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.
	US 7,993,835 BRCA2 mutations and use thereof (Risk of breast, ovarian and other cancers)	Claim 1: A method for detecting a mutation in a BRCA2 allele comprising: analyzing a BRCA2 nucleic acid from a sample obtained from a human subject; and detecting a mutation in said nucleic acid wherein said mutation results in the deletion of five nucleotides beginning at position 4,633 of a BRCA2 cDNA.
	US 5,508,167 Methods Of Screening For Alzheimer's Disease (APOE risk)	Claim 1: A method of detecting if a subject is at increased risk of developing late onset Alzheimer's disease (AD) comprising directly or indirectly: detecting the presence or absence of an apolipoprotein E type 4 isoform (ApoE4) in the subject; and observing whether or not the subject is at increased risk of developing late onset AD by observing if the presence of ApoE4 is or is not detected, wherein the presence of ApoE4 indicates said subject is at increased risk of developing late onset AD.
	US 7214483 KCNQ2 and KCNQ3, potassium channel genes mutated in benign familial neonatal convulsions (BFNC) and other epilepsies	Claim 1. A method for diagnosing the presence of a mutation in human KCNQ2 which causes BFNC or rolandic epilepsy wherein said method is performed by means which identify the presence of said mutation, [*lists specific mutations*]. Claim 2. The method of claim 1 wherein said means comprises sequencing human KCNQ2.

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