Mandating race: how the USPTO is forcing race into biotech patents

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Biotech patents have increasingly included race-specific claims since the completion of the Human Genome Project in 2003. The question of how and why this phenomenon is occurring was first addressed in these pages in November 2006 (ref. 1). At that time there appeared to be two basic forces at work: first, some inventors were using race defensively, to buttress broader claims not specific to race; second, others were using race affirmatively to capture race-specific markets. A more recent review of select patent prosecutions before the United States Patent and Trademark Office (USPTO) indicates a third and potentially more troubling dynamic at work: USPTO examiners are requiring applicants to include racial categories in the claims sections of some of their biotech patent submissions. The use of race in the claims section of a patent is particularly important because this is the legally operative section of a patent that defines the "metes and bounds," or territory, covered by the patent. The claims form the basis for subsequent research, development and marketing of products developed from the patent.

Race as requirement

The general contours of this phenomenon first came to light in December 2008, at a quarterly meeting of the USPTO's Biotechnology, Chemical and Pharmaceuticals (BCP) technology groups' 'customer partnership'. Among the presentations was one by USPTO quality assurance specialist Kathleen Bragdon titled, "A Look at Personalized Medicine"[2]. The presentation focused in particular on the patenting concept of "enablement," which requires that the written description of any invention shall be sufficiently clear as to "enable any person skilled in the art…to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention"[3]. To meet this requirement, the "full scope" of the patent claim must be enabled. The presentation noted that this requirement demands that an examiner reject a patent application if it fails to teach how to make and use the invention as broadly as claimed without undue experimentation. All this is fairly routine knowledge in the world of patents. The presentation, however, moved on to explore its application in the field of personalized medicine by using an example that explicitly implicated race as a requirement for patent approval. Specifically, as reported by John Aquino, of the *Life Sciences Law & Industry Report*, Bragdon went on to present a slide with the claim:

A method for treating a human subject having breast cancer, said method comprising: a) obtaining a nucleic acid sample from said human subject; b) subjecting the sample to PCR and identifying the nucleotide present at position 101 of SEQ ID NO:1; and c) treating the human subject with "breast cancer drug X" when a cytosine is detected at position 101 of SEQ ID NO:1 (ref. 4).

The specification in this example did not distinguish the race in the patients tested, it simply assumed 'human' to be the relevant category for the invention. Aquino notes, however, that the next slide began with the statement, "Prior art teaches that ethnicity is an unpredictable factor in single nucleotide polymorphism (SNP) correlation studies," and that studies published after the filing of the patent application indicated that "breast cancer drug X" was ineffective for African Americans. The analysis concluded that because effectiveness for all races was not established, "a scope of enablement rejection must be considered"[2]. There was a measure of push-back against this conclusion during the question and answer period after the presentation. Some noted that "African American" was a social, not biological, category and hence inappropriate grounds for rejection, particularly given the increasingly "multiracial" nature of US society. Another questioner pushed the logic of the conclusion to ask, "What if the data had said that the treatment was ineffective in left-handed Eskimos"[4]?

Following the controversy elicited by the race-specific example, the slides were replaced on the USPTO conference web site with slides using the phrase "patient populations" instead of race or ethnic-specific terms. Also, the statement that a "scope of enablement rejection must be considered" was modified to "The appropriateness of making any enablement rejection should be considered based on the foregoing facts"[4].

The presentation itself involved only a hypothetical patent application, and one might hope that the modifications following the critical response to the presentation indicated a reconsideration of the relevance of race to biotech patent claims. In looking at actual cases, however, one finds that, despite the push-back, the practice of requiring race continues, apparently unabated, at the USPTO. This is of critical importance, not only for inventors seeking to draft viable patent applications, but more broadly for our understanding of how racial categories are coming to play an increasingly significant role in biotech R&D. It also casts light on the great irony that as we claim to be making progress toward a promised land of personalized medicine, group categories of race seem to be gaining salience in both law and science.

The use of race in biotech patents is highly problematic because, among other things, it gives the imprimatur of the federal govern-

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ment to the misleading and potentially dangerous notion that race is a genetic category. Race is certainly relevant to understanding many biological conditions—the persistent reality of people of color suffering disproportionately high rates of morbidity and mortality for a wide array of conditions testify to this[5]. But such disparities indicate the complex interaction of race as a social and historical construct with biology. This is very different from the construction of race as a static and bounded genetic category in these patents. As a 2001 editorial in *Nature Genetics* put it, "scientists have long been saying that at the genetic level there is more variation between two individuals in the same population than between populations and that there is no biological basis for 'race'"[6]. Constructions of race as genetic are not only scientifically flawed, they are socially dangerous, opening the door to new forms of discrimination or the misallocation of scarce resources needed to address real health disparities.

Policy in practice

The initial observation of this phenomenon in 2006 was framed in relation to the US Food and Drug Administration (FDA)'s 2005 approval of the drug BiDil, the first pharmaceutical ever approved by the FDA with a race-specific application—for use to treat heart failure in "Blacks"[1]. BiDil was an example of race being used affirmatively to capture a specific market. In that situation, the race-specific patent underlying BiDil provided the impetus for garnering the race-specific approval from the FDA because it granted an additional 13 years of patent protection beyond an almost identical non-race-specific patent also held by BiDil's corporate sponsor, NitroMed. BiDil's situation, however, was quite distinctive—not least because it was a combination of two generic drugs, hydralazine and isosorbide dinitrate, that had been used to treat heart failure for over a decade.

Many other patents and applications use racial categories defensively; that is, to add additional support to a broader patent rather than explicitly frame an entire patent in terms of race. Typical in this regard is the patent, "Detection of susceptibility to autoimmune diseases," which specifies in its first claim that it applies to an "individual's risk for type 1 diabetes," and then goes on in claims two and three to cover first, an individual of "Asian descent," and then an individual of "Filipino descent"[7].

The logic of using race here is straightforward. Ideally, the inventors want the patent to cover their invention's use in any individual human being. Failing that (that is, if the broader claim is challenged), the inventors seek to have the narrower, but still substantial category of individuals of "Asian descent" covered; and, similarly, in the third claim, the still narrower category of "Filipino" is used as a final fallback.

Kathleen Bragdon's BCP presentation, however, raises a third set of issues. It indicates that race may be entering biotech patents not only as a defensive measure or, *á la* BiDil, as a means to capture a particular market, but as a response to demands placed upon the applicant by the USPTO itself. In these cases we see agents of the federal government requiring the introduction of race into biotech patents. Bragdon's presentation involved only a hypothetical case, but a review of some recent patent cases indicates that in actual practice USPTO examiners are requiring inventors to add race to their biotech patents.

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For example, while Bragdon was making her presentation, a case was pending before the Board of Patent Appeals and Interferences (BPAI) contesting a patent examiner's race-based rejection of an application covering a method of screening for a gene mutation that indicates an increased risk for prostate cancer. In that case the examiner had rejected an application, among other reasons, for failure to enable the full scope of the claimed method because it "has not [been] shown that the correlation between the claimed mutations and the risk of both sporadic and hereditary prostate cancers is significant in all populations"[8]. This finding, in turn, was apparently based on the application's disclosure that one of the relevant mutations was found in Caucasians, whereas another was found in African Americans. For the examiner, this meant that the same level of risk was not present in all racial populations, hence a lack of enablement. The examiner rejected the patent claims because the applicant did not differentiate risk by racial group but simply covered "a method of screening a subject"[9]. This is a real-life example of the exact same logic evident in Bragdon's presentation. The examiner here was denying a patent application for its failure to use race as a biological construct. To succeed, the applicants would either have to add race in a manner they did not think valid, or take the time and money to appeal the decision. In this case, they appealed, and won.

In its March 2009 decision reversing the examiner's rejection of the application, the BPAI found that, "It is unnecessary for Appellants to prove with 100% certainty that a correlation exists between the…mutations and an increased prostate cancer risk. It is sufficient that that the evidence is 'reasonably indicative' that a correlation is present"[8]. It concluded that "it is unnecessary for the claims to exclude all inoperative embodiments as long as the generic invention is enabled…"[8]; meaning that the same degree of risk need not be present in all races in order to make a claim to cover the method for use in a generic human subject.

One might hope that this commonsense result would send a message to USPTO examiners to reconsider their understandings of the place of race in biotech patents. Unfortunately, this has not been the case. In April 2010, another similar application rejection was also appealed. In this case, the application claimed a method of screening "a human individual" for genetic polymorphisms that might indicate a "predisposition to atopy" (an allergic hypersensitivity including such conditions as eczema and asthma). The patent examiner rejected the broad claim to cover a "human individual" primarily because the studies underlying the patent application had been conducted in "Caucasians" and "Asians." The examiner concluded, therefore, that the claim was only enabled as to these specific racial groups and not to humans in general. On June 18, 2010, the BPAI reversed the examiner's decision, noting that the fact that some of the claims "encompass other ethnic groups than Caucasian or Asian does not necessarily render these claims lacking in enablement," and finding that "a claim may encompass inoperative embodiments and still meet the enabling requirement"[10].

Between Bragdon's presentation and the multiple appeals, it is evident that the practice of requiring patent applicants to introduce race into their biotech patents has become routinized at the USPTO.

We might take solace in the apparent readiness of the BPAI to correct this errant behavior. But this will only take place if applicants have the wherewithal to continue the prosecution of their patent up through the appeals process. The BPAI opinions, therefore, are just the tip of the iceberg. One must ask how many applicants simply accede to the examiners' demands and incorporate racial categories into their patents to avoid the long, drawn-out process of appeal? In this regard, patent no. 6,716,581 (ref. 11),

covering a method to screen for a genetic polymorphism to help determine susceptibility to colorectal cancer, offers a cautionary tale.

The patent was issued in April 2004, long before Bragdon's BCP presentation. In the original application, filed in April 2001, the first claim read, "A kit for determining whether a subject has, or is at risk of developing, colorectal cancer wherein said kit is used to amplify and/or determine the molecular structure of at least a portion of the MnSOD gene." The application went on to enumerate a total of 35 claims, the very last of which introduced ethnicity, reading, "The method of claim 29; wherein the ethnicity of the subject is Hispanic." (Claim 29 covered individuals under 35 years old[12].) In this original form, the patent used Hispanic ethnicity, but in a defensive manner, much as the patent discussed above used the categories of Asian and Filipino. Here ethnicity seems to have been almost an afterthought, thrown in as the very last claim.

Yet, by the time the application had gone through the prosecution process, the examiner had effectively forced the applicants to reconfigure the patent to foreground ethnicity. As ultimately issued, the first claim of the patent begins, "A method of determining relative age-related risk of colorectal cancer in a Hispanic subject, comprising…"[11]. The examiner's objections to the early iterations of this application were much the same as those stated by the examiners in the later two applications discussed above that were successfully appealed. Thus for example, the examiner rejected several early claims stating that the specification, "while being enabling for methods for identifying increased risk of colon cancer in Hispanic subjects under the age of 35…does not reasonably provide enablement for methods wherein…the subjects [sic] is not Hispanic or is over 35"[13]. Stating an argument that clearly foreshadowed the logic of the Bragdon presentation, the examiner concluded, "Given the unpredictability in the art of genetic diagnosis, one cannot extrapolate the findings obtained with a single ethnic group to the general population"[14].

Most striking here in the examiner's logic is how she interpreted the issue of "unpredictability," exactly the opposite of how it should be understood with respect to race or ethnicity. Patent law holds that in the "unpredictable arts," such as genetics, greater specificity is required in the characterization of an invention to render it fully enabled[15]. The examiner's idea is that as genetic diagnosis is unpredictable, then its characterization in an application must be limited to the specific ethnic groups in which it has been practiced. This echoes the claim in Bradgon's slide that "ethnicity is an unpredictable factor in [SNP] correlation studies." This meant that correlations varied by ethnicity. But correlations vary across all sorts of categories. This is what the audience member at Bragdon's presentation meant when he referred to "left-handed Eskimos."

What both Bragdon and the examiner failed to consider, however, is that in the realm of genetics, race and ethnicity are more than just unpredictable "factors"; they are, in effect, "unpredictable arts," which themselves require specific definition if they are to be enabling. This is because race is not a coherent genetic concept. At best, it is, as Francis Collins has noted, a "weak and imperfect proxy" for genetic variation[16]. Race is best understood as a complex and dynamic social construct that is highly variable over time and across space—hence "unpredictable" when used in relation to genetics[17].

This is not to say that race cannot necessarily be used at all in biotech patents, but that its use should require genetically relevant specificity of definition and application, something more than mere self-identification—which is a social, not a genetic definition of race.

The applicants indicated a sense of this problem when they argued to the examiner that "there is no plausible scientific evidence to support any assertion that Hispanics differ from other groups" with respect to the substance covered by the application[18]. They tried to resist the imposition of ethnicity into their patent, noting that their choice "to perform their study in Hispanics, an underserved population whose involvement in medical studies should be encouraged, not used to impair Applicants' patent rights." Ultimately, however, they acceded to the examiner's demands rather than go through the appeals process.

Conclusions

The truly chilling aspect of this story are the questions it raises as to how many other applicants have given in to examiners' demands that they include race in their biotech patents? How many others have gone against their better scientific judgment to appease an examiner? The implications go far beyond the mere issuance of narrower patents. As evidenced in the example of NitroMed's BiDil, such patents can subsequently influence the design of clinical trials, the interpretations of the results and the marketing of end products.

The USPTO is currently undergoing a process of internal review and reorganization. Now is the time for it to confront head-on this misguided practice of injecting race into biotech patents. If race is to have a place in biotech patents it must not be casually imported as a social construct into biological contexts. Rather, any use of race—by applicant or examiner—must be rigorously defined and must clearly articulate and justify any purported relationship to underlying genetic attributes.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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