‘Extra’ genetic info—too much, too quickly?

Elizabeth Silverman

October 2013—In the 1997 film “Gattaca,” the movie-going public was introduced to a world in which biology was quite literally destiny. A world in which the probabilities encoded in one’s genome dictated virtually every aspect of one’s existence and where those found genetically wanting were relegated to society’s margins. Fortunately, genomics has so far yielded nothing so nefarious nor is it ever likely to, thanks in part to the vigorous debate that accompanies advances in genetic and genomic technologies. An example of this is the debate underway, and making medical news, among physicians, ethicists, and laboratory directors over the American College of Medical Genetics and Genomics’ recommendations on the reporting of incidental findings.

The dramatic decreases in the time and cost of DNA sequencing that have made it an increasingly practical clinical tool have also presented lab directors with a dilemma: What should be done with potentially clinically relevant genetic information generated in the course of diagnostic sequencing but not ordered by the physician? To the ACMG, the question was of sufficient magnitude to warrant establishing a standard, uniform policy to provide guidance. Accordingly, it convened a working group, and after 14 months of discussion, debate, analysis, and some external review, recommendations were published in March.

Dr. Voelkerding

The ACMG recommended that laboratories performing germline exome and genome clinical sequencing also analyze and report on pathogenic mutations in 56 carefully selected additional genes involved in a variety of serious diseases (see “The ACMG list”). The criteria for selection were that the diseases be both highly penetrant and actionable. The recommendations state that these incidental, or secondary, findings should be reported to the ordering physician as a matter of routine, regardless of the age of the patient or the nature of the original diagnostic order. Further, patients would not be asked to give informed consent for each gene individually; rather, they should be counseled about the possibility of receiving these incidental findings during the diagnostic informed consent process. The ACMG intends that the list of genes that constitute incidental findings will be reviewed regularly and modified as new data become available.

The controversy and debate over the recommendations began almost immediately. The issues that sparked the debate, however, were much broader and more far-reaching than the specifics of the chosen genes. With the possible exception of the *BRCA* genes, the debate has not centered on which genes were chosen so much as that any genes were chosen at all.

Critics of the ACMG recommendations argue that what the ACMG considers to be the reporting of incidental findings is actually the mandating of genetic screening because the findings cannot be incidental if they are actively searched for. The ACMG believes its recommendations are no different than the reporting of incidental findings that occur as a routine part of good medical care. They compare their recommendations to the situation in which a radiologist reports a suspicious shadow on a chest x-ray ordered for a fractured rib. Robert Klitzman, MD, associate professor of clinical psychiatry at Columbia University College of Physicians and Surgeons and the Mailman School of Public Health, counters in a July 24/31 *JAMA* “Viewpoint” that the situation is more akin to that of a radiologist adding an abdominal x-ray to an ordered chest x-ray and reporting findings on that as well. Karl

Voelkerding, MD, professor of pathology, University of Utah, and medical director for genomics and bioinformatics, ARUP Laboratories, weighs in squarely on the screening side of the issue: “There is a difference between screening and diagnostic mode—physicians order a test for a specific medical problem. The recommendations are screening.”

Critics argue that not only do the recommendations impose a burden on a laboratory to seek out and analyze variants for which there is no clinical basis or physician order, but it also must do so without the patient’s informed consent. If the whole genome must be sequenced to, for example, identify the cause of a child’s disabilities, then the 56 mutations will be analyzed, whether the clinician or patient—or the patient’s surrogate in the case of a child—wants or orders it or consents, says Lainie Friedman Ross, MD, PhD, Carolyn and Matthew Bucksbaum professor of clinical medical ethics at the University of Chicago and associate director of the MacLean Center for Medical Ethics. Dr. Ross feels strongly that what is being done is not clinical medicine but screening research—because the significance of these genes in the low-risk population has not been well explored—and that, as she told CAP TODAY and is sure to provoke sharp response, “Doing research without informed consent is conscripting people to be research subjects.”

Dr. Green

Most of those on both sides of the debate acknowledge the impracticality of counseling and obtaining informed consent for each of the 56 genes. “It is not practical to offer a Chinese menu of options to a patient—it is neither appropriate nor feasible,” says Robert Green, MD, MPH, lead author of the ACMG recommendations and associate professor of medicine, Division of Genetics, Brigham and Women’s Hospital and Harvard Medical School, and associate director for research, Partners HealthCare Center for Personalized Genetic Medicine. ARUP’s Dr. Voelkerding agrees that “Informed consent is a challenge in such a complex area,” but adds, “Complexity should not rule the day.”

A key and perhaps defining issue that colors almost all aspects of the debate, including that of informed consent, revolves around the speed and evolution of diagnostic sequencing technology. Many laboratories now test for genes on a disease panel basis, and even those that do exome sequencing often conduct bioinformatics analyses for each disease separately. However, this is unlikely to be the situation in the near future. Dr. Green explains: “The amount of extra labor will dramatically decrease in the coming years—the recommendations weren’t developed for the next three months; they were developed for the future. Very quickly all genomic information will be revealed by the bioinformatics pipeline that is being developed. Testing will quickly become one test. The information that is uncovered could be life-saving.”

Dr. McGuire

Amy McGuire, JD, PhD, a member of the ACMG working group and Leon Jaworski professor of biomedical ethics and director of the Center for Medical Ethics and Health Policy, Baylor College of Medicine, sums up the issue: “The ACMG has always been in favor of thorough informed consent. The debate turns on how you view the technical

issues: whether you view it as a single test whose scope of analysis is up to the experts or whether you see it as separate tests that need informed consent for each." Her own view: It's a single test, and the debate is over scope of analysis, not additional testing or screening.

One of the most forceful technical arguments against the recommendations is that, although they are predicated on the selection of highly penetrant genes, the penetrance data are flawed. The data the ACMG used were obtained from high-risk populations, whereas penetrance in the general population—the population in question—is likely to be lower. How much lower, no one knows. The consequences of returning a positive finding on a gene that turns out to have lower than expected penetrance are potentially far-reaching. Patients with positive findings may be referred on for costly or invasive tests and procedures that could cause physical harm and excess anxiety and result in a lifetime of unnecessary medical surveillance. However, James R. Lupski, MD, PhD, DSc, Cullen professor and vice chair of genetics at Baylor College of Medicine, argues that not reporting these variants to the referring physician means he or she isn't given the opportunity "to contextualize the information into a differential diagnosis enabling a management/treatment plan" and potentially denies the patient a chance at life-saving therapies.

Robert L. Nussbaum, MD, chief of the Division of Genomic Medicine, Department of Medicine and UCSF Institute for Human Genetics, says until he sees evidence to the contrary, he would expect well-vetted pathogenic mutations identified in families to be a major risk for someone who carries one, regardless of how it was found. "We know, for example, the penetrance of *BRCA1/2* mutations in high-risk families with multiple affecteds is somewhat higher than in patients ascertained through population screening, but the risks are still very high."

The ACMG acknowledges the lack of penetrance data for the general population and that it does expect these to be lower than for high-risk populations. However, it foresees that the listed genes will be reviewed and subject to modification regularly as more data on penetrance and other issues are accumulated. Its view is that the question of what laboratories should do with incidental findings exists today and needs to be addressed today, especially as the magnitude of the problem will grow as gene sequencing increasingly becomes part of medical practice. "Thousands of exomes and genomes will be sequenced clinically in the coming year," Dr. Green points out.

Other technical issues raise objections too: for instance, that negative findings do not necessarily mean that patients are not at risk and that negative results may give patients a false sense of security. Sherri Bale, PhD, managing director of GeneDx, speaking on an Association for Molecular Pathology webinar on Sept. 17, pointed out that the recommendations do not address pathogenic structural variants and that, as an example, 28 percent of Von Hippel Lindau cases are due to a complete or partial deletion. Additionally, there are sequencing coverage issues with several of the listed genes, all of which have the potential to result in false-negatives. Then, too, results between labs may vary, particularly when different technologies are used.

That tests are not perfect is not a new idea, says Dr. Nussbaum, a member of the ACMG working group, nor is it difficult for patients to understand. "We have been having this discussion for decades around prenatal chromosome testing," he says. "Patients understand, with counseling, that prenatal karyotyping would not ensure the birth of a child without any genetic or other birth defect."

There is an almost universal acknowledgement that more research is needed to resolve many of these concerns, but the question of whether the ACMG recommendations were timely or premature remains a subject of intense debate.

No set of issues stemming from the ACMG recommendations arouses quite the depth of feeling as those related to patient autonomy and ethics. To the extent that the recommendations call for the automatic reporting of findings not ordered by a physician and not specifically consented to by a patient, critics see an abrogation of the enshrined principle of a patient's right not to know. "This is a risk-benefit calculation that should not be imposed," says Dr. Ross of the University of Chicago. Megan Allyse, PhD, postdoctoral fellow at Duke University's Institute for Genome Science and Policy, says, "Patients should have access and information that they want and not information that other people think they should have." Their comments represent a broad swath of ethical opinion.

Those with concerns about the ethics of what has been recommended believe their argument is strengthened by

the fact that compulsory reporting of incidental findings applies not only to the patient undergoing clinical sequencing but also to any individual, such as parents or siblings, whose DNA is being sequenced for use as a control. None of these individuals would have a choice about whether to receive incidental findings despite their not being the patient. Moreover, the all-or-nothing nature of the recommendations means patients who do not wish to have information on the 56 genes would not be candidates for clinical DNA sequencing. They would have to forego diagnostic testing or find a way to obtain the testing by another modality, if available.

Dr. Grody

The recommendations also affect the autonomy of the ordering physician who may now be forced to counsel patients on a matter wholly unrelated to that which brought them to his or her office or to refer them for additional counseling or further testing or both. Critics of the recommendations cite the shortage and expense of genetic counselors as a purely practical impediment to carrying out the ACMG recommendations. Although the ACMG estimates that positive findings would affect one percent of patients and therefore not impose an undue burden, especially in light of the potential benefits, Dr. Bale noted that anecdotally lab directors are seeing rates of positive findings that exceed five percent. Wayne Grody, MD, PhD, professor of pathology and laboratory medicine, pediatrics, and human genetics at UCLA School of Medicine, asks, “Can you force the lab director to do something they are not comfortable with? The recommendations may be asking a little too much of lab directors.” He offers patients an opt-out in his laboratory, as do some other labs. Says Columbia’s Dr. Klitzman, “It is unclear whether physicians, labs, and hospitals are ready for this type of testing.”

Laboratories find disease-causing variants in the course of exome and genome analysis, even when not explicitly looking for those variants, and being asked to withhold findings puts labs in a difficult spot, says Heidi Rehm, PhD, director of the Partners Healthcare Laboratory for Molecular Medicine, Cambridge, Mass., and a member of the ACMG working group. “We find that families are asking for these results and are even surprised we would consider not returning them.”

Dr. Joffe

Also controversial is the reporting of adult onset diseases to the parents of pediatric patients. Here there is concern that the information is not immediately actionable and that patient autonomy would be infringed when the patient is too young to offer informed consent. There is also the fear that this information may affect how parents view their child. However, as pediatric oncologist Steve Joffe, MD, MPH, Emanuel and Robert Hart associate professor and director of the Penn fellowship in advanced biomedical ethics, Department of Medical Ethics and Health Policy, University of Pennsylvania Perelman School of Medicine, points out: “There is scant data to address that question. We don’t know what impact it will have, and there are no data to support any conclusions.” The traditional guidelines of waiting until a child is an adult to offer him or her testing for the predisposition to an adult onset condition are overly restrictive, in his view, and should be revisited when there are actionable gene variants, independent of age of onset. He cites the net medical benefit of alerting a child’s family to a risk they might otherwise not have known about and the secondary benefit to other family members. His primary concern with the

ACMG's recommendations is technical in nature: the difficulty of determining what constitutes a pathogenic variant.

Another issue is the degree to which parents want or are capable of receiving information about an additional, potential illness while in the midst of dealing with the condition that brought their child to the sequencing lab in the first place. Dr. Voelkerding asks, "Do parents really want information on the genes on the list when they are worried about a specific problem their child has? One has to respect patient and family autonomy and guard against paternalism in medicine." Also difficult, Dr. Grody says, is when parents have to be informed that the diagnostic sequencing did not provide an answer but that the sequencing did uncover an unrelated problem. Will parents want to know or even be able to process such extraneous information?

The problem of coping with the extra information applies to adults as well. Says Dr. Klitzman: "The one-size-fits-all policy is not always the best. Someone undergoing sequencing for metastatic breast cancer may not want to know about these other things that may be wrong with them."

All of these cogent and well-reasoned arguments must be balanced against ethical arguments related to having the ability to discover and deliver potentially life-saving information and not using it. The arguments are strengthened if one believes that genome and exome sequencing are likely to become one comprehensive test with one bioinformatics readout in the not too distant future.

Although the ACMG recommendations do not address financial and reimbursement issues, these will certainly have an impact on the medical community's ability to carry them out. Physicians worry about the financial burden of genetic counseling, which is not always covered by insurance, and of followup testing and the resulting treatment or surveillance. The costs could make following the recommendations prohibitive. "We don't have unlimited health care dollars," Dr. Voelkerding says. "There should be continued discussion and research to better understand how to best apply this expensive technology in terms of clinical practice and to determine its true cost benefit."

For the lab director as well, the recommendations could have significant financial consequences. The recommendations specify what genes to report on but not which variants. Dr. Bale estimates that it takes one-half hour to three hours to search databases, download purchased papers, read and review the papers, and interpret the data. Her lab confirms positive findings with Sanger sequencing, which takes several days. There is no billing code that covers the reporting of secondary findings and no obvious way to get paid for the extra work. She worries about whether labs will incur increased legal liability for reporting or not reporting the recommended findings. This is especially true since *BRCA* testing is on the list and still the subject of litigation.

Added to the issues for which there is consensus—the need for more data, the likelihood of penetrance being lower in the general population, and the impracticality of informed consent for all 56 genes—there is general agreement that implementing the recommendations is going to highlight the need for more education of physicians and patients. Historically, genetics has been subject to medical exceptionalism and physicians referred cases involving genetics to geneticists and genetic counselors. This reflected an era when most available genetic information was associated with narrow but difficult areas largely restricted to reproductive matters and rare diseases often seen in pediatrics. Physicians and patients were unlikely to have encountered many other health issues related to genetics, and physicians relied on the specialized training of genetic counselors to help patients understand and absorb the information.

However, as genetic information moves into mainstream clinical practice, most notably in oncology, it raises the questions, what is so unique about the genome and does it merit continued exceptionalism? Physicians, after all, have a wealth of experience in contextualizing diagnostic information and helping patients understand complex medical conditions. Patients rely on the expertise of their physicians in the selection of diagnostic tests without any special counseling. Tests to diagnose one medical problem sometimes result in finding others.

It is therefore likely that the exceptionalism that requires the use of specialized geneticists and genetic counselors in every case, for all situations, will gradually decline over time. This is particularly true as more data are accumulated and genetic information becomes more actionable and perhaps less of an enigma to patients.

Physicians will, however, need to be brought up to speed and patients made more comfortable with the positive impact that genetic information can have on their health. The educational aspects of the field may be no easy task considering that most physicians attended medical school before the initial $3 billion genome was sequenced in 2003. The question of how this extra education is going to be achieved and in what time frame also forms part of the current debate to the extent that the ACMG recommendations are a step toward the clinical mainstreaming of genetic and genomic information.

The ACMG recommendations have caused discomfort in other ways. There is a feeling that they are too rigid and that results should be reported on a case-by-case basis in consultation with the ordering physician. No one is opposed to patients receiving the information, the argument goes, but the way the recommendations are written allows little wiggle room for individual patient situations; this may place an undue burden on the ordering physician who has to make the ultimate decision about which findings, if any, to share with the patient. Some feel this is a bridge too far too fast. “In conventional medicine the need for tests drives the use of the test,” Dr. Klitzman says. “With genetics this is not the case—the technology is driving the use.” While the rapid decline in the cost of sequencing and the flow of new products and easier–to-use instrumentation make sequencing increasingly practical as a clinical tool, some question whether the advances in technology have outstripped the medical community’s ability to understand and integrate the results into the medical mainstream.

There is wide agreement that the debate over the recommendations is a positive development and that genetic information and technology bring with it many difficult questions that are not easily answered. Nevertheless, there is also a feeling that there was not enough debate before the recommendations were released. “I am glad that there is a healthy and vigorous debate,” Dr. Voelkerding says, “but it’s unfortunate that it’s post hoc with respect to the recommendations being released.” He says they were insufficiently vetted by all relevant stakeholders and therefore were premature, “as evidenced by the current debate.” Others feel that the recommendations are premature because more research needs to be done. But in the ACMG’s view, calling for more research does not address the current problem of providing guidance, however preliminary, to laboratory directors who uncover abnormal findings. Says Dr. Green: “Incidental findings cannot be hidden away or the responsibility shifted to the patient. The data are not perfect—everyone agrees, but it is not an ethical question. It is an ethical and medical imperative to report the results.”

“Do no harm” is getting harder to define in the age of molecular medicine. Individuals on all sides of the current argument strongly believe they have the patient’s best interests at heart and that harm might be done by either following or not following the recommendations. Are the recommendations forward-thinking and visionary or do they represent the views of a more academic style of medicine that overlooks important clinical practicalities? There is no easy answer but the debate itself is part of an important process. Whether the recommendations represent a step forward into the genomic future or backward into the paternalistic past, it remains unarguable that it is the singular goal of all medicine—molecular or otherwise—to assess, analyze, and act on clinical findings to ensure that biology is not inexorably destiny. And we can all rest easy that those who make their voices heard, today and in the future, guarantee that “Gattaca” will forever remain just an entertaining piece of science fiction.

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The ACMG List

Hereditary breast and ovarian cancer *BRCA1&2*
Li-Fraumeni syndrome *TP53*
Peutz-Jeghers syndrome *STK11*
Lynch syndrome *MLH1, MSH2, MSH6, PMS2*
Familial adenomatous polyposis *APC*
MYH-associated polyposis; adenomas, multiple colorectal, FAP type 2; colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas *MUTYH*
Von Hippel Lindau syndrome *VHL*
Multiple endocrine neoplasia type 1 *MEN1*

Multiple endocrine neoplasia type 2 *RET*
Familial medullary thyroid cancer *RET*
PTEN hamartoma tumor syndrome *PTEN*
Retinoblastoma *RB1*
Hereditary paraganglioma-pheochromocytoma syndrome *SDHD, SDHAF2, SDHC, SDHB*
Tuberous sclerosis complex *TSC1, TSC2*
WT1-related Wilms tumor *WT1*
Neurofibromatosis type 2 *NF2*
Ehlers-Danlos syndrome, vascular type *COL3A1*
Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections *FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYLK, MYH11*
Hypertrophic cardiomyopathy, dilated cardiomyopathy *MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA*
Catecholaminergic polymorphic ventricular tachycardia *RYR2*
Arrhythmogenic right ventricular cardiomyopathy *PKP2, DSP, TMEM43, DSG2*
Romano-Ward long QT syndrome types 1, 2 and 3, Brugada syndrome *KCNQ1, KCNH2, SCN5A*
Familial hypercholesterolemia *LDLR, APOB, PCSK9*
Malignant hyperthermia susceptibility *RYR1, CACNA1S*