Opinions

Ethical Issues in Precision Pathology

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Abstract: With a growing role of precision pathology in the healthcare system, pathologists are facing more ethical issues and challenges. These include but are not limited to: autonomy versus social responsibility; reporting genes with unknown functions; the right to know the results and to be tested; healthcare disparity; what represents the standard of care; prenatal test and the fetus's right; genetic discrimination and eugenics, etc. New medical and ethical standards need to be established to guide the practice of precision pathology.

Keywords: Ethical issues, Precision pathology

Introduction

Since its inception in 2011, precision medicine has been endowed with bioethical implications [1]. Research initiative have been designed to address the bioethical issues, such as the health disparity, privacy and security [2, 3]. Last decade has seen hot debates over the bioethics of precision medicine [4], and some bioethical concerns have also spilled over to precision pathology.

Traditionally pathologists seem to assume little ethical responsibilities other than reporting the laboratory results without violating the patient privacy and confidentiality and to leave the difficult clinical decisions to clinicians. With more involvement in the shared clinical decision-making processes and more patients ordering genetic tests directly from the laboratories, pathologists are involuntarily involved in ethical decisions, such as reporting genetic results of unknown clinical significance, who should know the genetic results other than the ordering patient, and the social and economic implications of the genetic results, etc.

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Autonomy *vs.* Social Responsibility

Beauchamp described the four principles approach to the health care ethics [5]. They consist of beneficence, maleficence, autonomy, and justice. Patient autonomy and new regulations [6, 7] enable patients to order genetic tests directly from the laboratories without prescription by the primary care providers. With enormous marketing efforts on TV, print advertisement, and the Internet by the booming Direct-to-Consumer Genetic Testing (DTC-GT) laboratories, genetic testing becomes a commodity rather than a diagnostic tool. The testing results are commonly used for predictions about health, providing information about common traits, and offering clues for a person's ancestry. But it is not as simple as getting a flu shot, it has much more serious implications, such as interpretation of the testing results are not always straight forward since the functions of many genes are still yet to be defined; the genetic results affect not only the subject who orders the test, but also

the subject's closest relatives, such as the siblings and children who may or may not want to know the genetic results; certain genetic diseases may lead to increased premium for health insurance and life insurance. Certain genetic abnormalities may be utilized for legal defense of certain crimes. If disclosed, the genetic information may also affect the subject's employment and promotions, etc.

Genes with Unknown Functions

Remarkable advancement of technologies such as the next generation sequencing (NGS) technologies can generate large amounts of data and identify numerous variant mutations in a matter of days, but our current knowledge on the clinical significance of some variants is lagging far behind. These Variants of Uncertain Significance (VUS) can be identified in genes with known functions or genes with no known functions. Some VUS may be relevant to the purpose for sequencing, whereas others may be unrelated to the original rationale for sequencing the patient. Some unknown VUS may have clinical significance and deserve further investigation while others might just reflect polymorphism of little significance. Vears et al. surveyed 27 laboratory personnel, representing 24 laboratories in Europe, Canada and Australia, and they found variation in the reporting practices of VUS across the laboratories within the study [8]. To avoid this reporting dilemma, many commercial laboratories choose to sequence limited number of genes in their panels, which largely consist of the genes with well-known functions (Foundation Medicine). Although there is no consensus as to which VUS should or should not be on their reports, standards and guidelines have been established by a jointed effort by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology for interpreting the VUS [9]. However, large variations in reporting policies still exist between laboratories in the world [10].

Right to Know and/or to Be Tested

This issue may sound silly because the answer seems so obvious, but not really. Almost all the diseases are caused by two factors: 1) the intrinsic cause from the human body; 2) the extrinsic environmental factor(s) including radiation, toxicity, and biohazard pathogens. Although lifestyle can change the condition of our bodies to some extent, what we cannot change are the genetic makeups we inherited from our parents. As we are aware that we are sick because we are genetically liable to diseases, the genetic information will always have some implications, particularly for some diseases with serious disability and fatality. One extreme example is the prion disease. When a PRNP variant has been detected in an index case, should the relatives be informed and/or tested as well?

A small study showed that anxiety rates were high and similar between the noncarriers and untested subjects when they were told the risk of a devastating genetic disease. Whether the relatives were informed and/or tested or not did not seem to make a difference [11]. Amyotrophic lateral sclerosis (ALS) is another devastating genetic disease. Since its familiar forms and the sporadic forms are clinically indistinguishable and over 30 genetic mutations have been linked to the familiar forms and rarely the sporadic forms, identification of a mutation in one family member will lead to the request for testing from relatives who are eager to know their own individual risk to develop ALS [12].

Cancer is a genetic malignancy and *BRCA1*, *BRCA2*, and *TP53* mutations have been implied in the lifetime high risk of breast cancer development [13]. Although it is well accepted in the Western world that mastectomy and salpingo-oophorectomy are used to lower the risk of breast cancer and ovarian cancer in patients with mutations in those genes [14], in Asian countries, family members may hesitate to be genetically tested for those mutations for the following reasons: high costs of tests; perceived lack of ability to cope with test results; and insuffi-

cient information about genetic testing [15].

Healthcare Disparity

Owing to the innovations in NGS, we have seen a marked decrease in the costs of genetic testing. As compared to the routine chemistry and hematology tests, genetic tests remain expensive. Most insurance companies either entirely or partially cover the costs of genetic testing if the tests are requested by the health care providers. Medicare and Medicaid usually also cover the medically indicated genetic tests. However, the DTC genetic tests are usually paid by the patients out of their own pockets.

Because of this, genetic tests are a luxury of the rich and the low-income families cannot afford the expensive genetic tests unless it is medically indicated. When a mutation variant is identified in a rich person, the poor relatives will not be able to access their own genetic information even though with huge anxiety. Inequality and injustice are among the ethical issues of precision pathology.

Whole genome sequencing (WGS) is no longer a dream and can be performed for $100 [16]. Laboratory developed tests (LDTs) will play an important role in this endeavor and become a target for regulation by U.S. Food and Drug Administration (FDA), Congress, and other stakeholders [17]. Whether WGS routinely performed on all the newborns should be a standard of care will be the next challenge facing the regulatory agencies. Changes of coding and coverage which lead to lower reimbursement may also impose a financial burden on the testing clinical laboratories and thus hinder patient access to genetic tests [18].

Standard Care

On September 18, 2019, Congressman Eric Swalwell reintroduced the bipartisan bill *Advancing Access to Precision Medicine Act* [19], which would pilot-test whether Medicaid coverage of a variety of types of genetic and genomic sequencing for children can help settle their diagnostic challenges, improve clinical outcomes, and ultimately reduce program expenditures. On January 27, 2020, CMS announced that NGS for beneficiaries with inherited ovarian or breast cancer will be covered by Medicare [20]. Currently only genetic tests for certain diseases have become the standard of care and can be reimbursed by Medicare and Medicaid. One universal genetic test should be the WGS for all the newborns whether they have insurance coverage or not. This approach will identify all the harmful mutations at the beginning of life and many diseases can be prevented and treated early. For example, the glucose-6-phosphate dehydrogenase (G6PD) deficiency disease, if detected early, can be prevented by avoiding oxidative stressors [21], or corrected by CRISPERS as in sickle cell disease [22]. Similar approach can be used for other hemoglobinopathies, such as hemoglobin S/C disease and hemoglobin S/β+ thalassemia, etc. Gene mutations with liability to cardiovascular diseases and hypertension can be prevented by adopting a healthy lifestyle in early life. Detection of mutations in oncogenes and tumor suppressor genes may also enable us to start the surveillance early, manage the tumor properly, and prolong the patient's life expectancy.

Prenatal Tests and the Fetus's Right

There are lots of debates over the fetal rights [23]. Prenatal genetic tests are currently utilized to identify fetuses with genetic defects and prevent the birth of unhealthy children such as Down syndrome and other overt inherited genetic diseases. With the booming DTC-GT services, parent(s) may request WGS directly from the laboratories to look for certain genetic diseases in order to make the decision of abortion [23]. Then the fetus's right will be challenged. Genetic tests could be used to identify fetus as a result of adultery and cause tensions between the legal partners [24]. Prenatal genetic tests have also been used by parents in some cultures to se-

lect the fetus of the male gender [25], leading to imbalanced gender distribution in the population.

Genetic Discrimination and Eugenics

There are no “good" or “bad" genes, but some genes may be associated with more desirable features or healthy traits, whereas other genes may be associated with health risks. If disclosed, the individuals with “undesirable" genes may be discriminated, hard to have a relationship, difficult to find a job, and declined of certain health and life insurances. Although genetic information can be utilized to improve the health and quality of life of individuals and is being used to select embryos when employing *in vitro* fertilization [26], but this information could also be used by some people to control the “undesirable populations” [27] and provide a ground for racists and Nazis [28]. Eugenics for “desirable" features will eventually abolish genetic diversity, which is entirely undesirable by mankind.

Conclusion

With more involvement in clinical decision making, precision pathologists will share more ethical responsibilities with their clinical partners. They will seek informed consents from patients for molecular tests, select tissue source for diagnostic studies, choose gene panels and select analyzing methodologies, recommend drugs and dosages for therapy, monitor therapeutic efficacy and adverse effects, and evaluate clinical outcomes and document any undesirable reactions. Since medicine is individualized, each individual patient will have a unique pathological analysis and therapy. New medical and ethical standards need to be established to apply to this newly emerging discipline.

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