Ethical Aspects of Molecular Pathology

Overview
Molecular diagnostics plays an increasingly prominent role in pathologic diagnosis. Ethical considerations are at play in each step of designing, implementing, and interpreting molecular testing, as well as translating this testing to clinical decision-making. Patients benefit from improved diagnostic accuracy and improved ability to identify personalized biomarkers that inform their treatment and prognosis. However, these tests carry risks to patients, including the risk of false positives or negatives, the possibility of incidental results, and the retention of genetic data that may be re-evaluated in the future or shared with other parties. These benefits and risks must be appropriately understood in the context of informed consent, a task that is complicated by the fact that the ordering pathologist typically does not interact with the patient. Finally, considerations of justice are driven by the increasing complexity and cost of diagnostic testing, which can result in unequal distribution of care and resources.

Learning Objectives
- Apply principles of beneficence, non-maleficence, autonomy, and justice to the implementation and interpretation of molecular testing in a pathology laboratory
- Differentiate the ethical considerations arising in germline molecular testing from those in tumor diagnostics
- Design approaches for navigating common ethical situations that arise in molecular pathology

Pre-Reading Assignment

Brothers KB and Rothstein MA. Ethical, legal and social implications of incorporating personalized medicine into healthcare. *Per. Med.* (2015) 12:1, 43-51.

Cushman-Vokoun A et al. Laboratory and Clinical Implications of Incidental and Secondary Germline Findings During Tumor Testing. *Arch Pathol. Lab Med.* (2022) 146: 70-77.

Vos, S et al. Ethical considerations for modern molecular pathology. *J. Pathol.* (2018); 246:405-414.

Pre-activity Lecture

Conway. “Ethical Aspects of Molecular Pathology” (recorded lecture)

Case-based Activity
- Case 1 Vignette
    - A 49-year-old woman with a family history of lung, prostate, and ovarian cancer submits a DNA sample to a company that performs cancer susceptibility testing in addition to ancestry determination. She and her sister did so primarily to learn about their genetic ancestry together. They are asked to sign consent forms allowing the company to share de-identified data with other corporate and academic institutions. The form provides information about the risks and benefits of the testing, but a face-to-face interaction is not part of the discussion.
        - **Do the sisters understand their risk for an inherited gene that causes cancer?**
        - **What should their informed consent process include?**

        - **Suppose their genetic testing identifies a gene associated with a predisposition to cancer. What factors should be weighed in considering the relevant benefits and risks to the sisters?**

- Case 2 Vignette and Discussion Questions
    - A 22 year-old man is diagnosed with a low-grade brain tumor. Extensive molecular testing, including a next generation sequencing (NGS) panel identifies only a mutation in the *FGFR1* gene that is determined, based on a review of the literature and genetic databases to be a variant of uncertain significance (VUS). His tumor is considered benign, but classified as "not otherwise specified." Four years later, his tumor recurs. Molecular testing performed at another institution identifies the same variant in the *FGFR1* gene, which is now confirmed based on new studies to be pathogenic. The identification of this *FGFR1* alteration is brought to your attention by the patient's treating oncologist at your multidisciplinary tumor board. Identification allows more precise classification of the tumor; although treatment likely would have remained the same, classification as likely pathogenic renders the patient eligible for a clinical trial of targeted therapy.
        - **What are the relevant appropriate procedures to have in place regarding reporting, storage, and re-review of molecular data?**
        - **What are the relative benefits and costs associated with re-reviewing previously reported molecular data?**
        - **Whose clinical responsibility is it to raise the issue of a potential change in the clinical significance of a previous molecular finding?**

- Case 3 Vignette and Discussion Questions
    - World Health Organization (WHO) criteria identify deletion of the *CDKN2A* gene as a biomarker that indicates poor prognosis in meningioma, a common form of brain tumor. You estimate that roughly 1-2% of tumors you test will harbor this alteration. The identification of this alteration carries significant prognostic implications, but treatment guidelines are not established. The WHO does not specify an assay for identifying this alteration, and your laboratory has tasked you with choosing the most appropriate procedure for interrogating it. Your options for testing include:

        (1) immunohistochemistry (IHC) evaluating loss of a secondary protein as a proxy for *CDKN2A* deletion (low cost, low sensitivity)
        (2) Fluorescence in-situ hybridization (FISH) testing evaluating only for *CDKN2A* deletion (intermediate sensitivity and cost)
        (3) Chromosomal microarray (CMA) testing, which evaluates genome-wide chromosomal changes, including *CDNK2A* deletion (highest cost and highest sensitivity).

        - **Which assay to you recommend for testing for CDNK2A/B deletion, and what factors are implicated in this decision?**
        - **How do considerations of patient autonomy influence this decision, and how do you incorporate these considerations?**
        - **How should you incorporate input from your colleagues in neuro-oncology, radiation oncology and neurosurgery?**