PEDIATRIC AND MATERNAL-FETAL DIVISION NEWS
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AACC Better health through laboratory medicine.

FROM THE MIND OF THE CHAIR

Happy New Year!

I am honored to serve as the PMF Division Chair for the next 2 years. I would like to thank Dr. Alison Woodworth for her hard work and leadership as Chair over the last 2 years. Thank you also to our outgoing board members, Christina Lockwood (Secretary), Amy Pyle-Eiola (Treasurer), and Shannon Haymond (Past Chair) for all your contributions to the Division.

Our division has many exciting projects planned for 2020, including a continued involvement in projects to establish pediatric reference intervals and examine proper test utilization. As always, we welcome volunteers to become involved in these endeavors, so please contact a board member if you are interested in participating.

In this issue of the newsletter, we are up to E in The ABCs of Pediatric Laboratory Medicine, and E is for Ethical Issues in Laboratory Medicine. Our Interview with a Distinguished Colleague features Dr. Uttam Garg, the 2019 winner of the Outstanding Contributions to Pediatric and Maternal Fetal Clinical Chemistry. Excerpts from the literature highlights an article on newborn genetic sequencing, and the issue is rounded out with the announcement of our newly elected board members.

I hope you enjoy this edition of the newsletter. Please keep your eye on the division Artery page for interesting discussions and announcements of activities at the upcoming annual meeting.

Angela Ferguson

Chair, AACC PMF Division

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THE ABC'S OF PEDIATRIC LABORATORY MEDICINE:

"E" is for Ethical Issues in Laboratory Medicine

Ann M. Gronowski, PhD
Department of Pathology, and Immunology, Washington University School of Medicine in St. Louis, St. Louis, MO

Melissa Budelier, PhD
Department of Pathology, and Immunology, Washington University School of Medicine in St. Louis, St. Louis, MO

Sheldon Campbell, MD, PhD
Department of Laboratory Medicine, Yale University School of Medicine, New Haven, CT

Laboratorians, like other medical professionals, must adhere to high ethical standards. However, many clinical laboratory training programs do not teach medical ethics (1). The terms 'medical ethics' and 'biomedical ethics' are often used interchangeably and can be defined as "a system of moral principles that apply values to the practice of clinical medicine and in scientific research" (2). The development of modern biomedical ethics was largely a response to grossly unethical behavior (For a more in-depth review, see reference 3).

The core principles of biomedical ethics include:

- Respect for autonomy,
- Beneficence (doing good),
- Non-maleficence (avoiding harm), and
- Justice (4).

Applications of these principles include use of informed consent, assessment of risks and benefits, and equitable treatment and allocation of resources. These principles can be applied to both medical research and medical practice.

Informed Consent

Respect for autonomy requires that people are given the opportunity to choose what happens to them. This opportunity is given, among other ways, when they are provided informed consent. Patients must be fully informed about why they are having samples collected, what testing will be performed, the potential risks and benefits, give consent freely, and have the right to withdraw consent at any time. There may be exceptions for persons who are unable to give consent such as unconscious patients, children, and mentally impaired persons. In some cases, family members or guardians may be able to provide consent in lieu of the patient.

Clinical laboratory testing is usually ordered by a physician and consent is often implied. If laboratorians become aware that a patient has refused testing they have a duty to investigate and potentially refuse to perform testing. Consultation with the clinical team is useful when consent is questionable.

When a patient refuses testing that heath-providers believe is needed an ethical dilemma is created. Refusal of drug testing for fear of repercussions, and declining blood products due to religious beliefs are two such

examples. Justifying actions that violate ethical principles requires consideration of whether the proposed action: 1) is likely to achieve the underlying goal, 2) presents the lowest degree of infringement, 3) minimizes any negative consequences, 4) has no morally preferable options, and 5) was arrived at through the proper process (5).

Leftover Specimens

In the U.S., the Common Rule permits research using tissue without patient consent in certain circumstances. Clinical laboratories are allowed to use specimens without consent for the purposes of healthcare operations (6). In addition, an Institutional Review Board (IRB) has discretion to waive or alter informed consent requirements if the IRB finds that the research meets certain criteria such as minimal risk to the subjects, or the research could not practicably be carried out without the waiver or alteration (6). When using leftover specimens for research, risk may be minimized by removing patient identifiers.

Genetic Testing

Numerous ethical concerns surround genetic testing, because it can reveal intensely personal information which may impact both the patient and the patient's family. The results of genetic tests may affect the lives and relationships of parents, siblings, children and even extended family members.

The right to autonomy should allow people to have genetic testing performed, if they so choose. At the same time, autonomy would allow people who do *not* want to know about their diagnosis or risk for disease the right to decline testing, even if physician-ordered. However, some genetic testing, such as newborn screening, is performed automatically without physician orders (usually required by public health codes). The idea is that because the diseases detected are treatable, the benefit to the public outweighs the autonomy of the individual. Because genetic testing can reveal heritable disorders that may affect other family members, once a disease or risk for disease is detected, patients and physicians are faced with the ethical dilemma of informing other family members. Genetic testing may impact an individual's ability to obtain life or disability insurance. Hence, a discussion of the potential impact on the patient and family should be undertaken before testing is performed.

There are many questions of justice around genetic testing. For instance, who has access to expensive procedures such as pre-implantation genetic diagnosis? Should only those with financial means be able to screen for devastating diseases prenatally? Should parents be allowed to test children for diseases for which there is no treatment? Because prenatal screening is used to choose termination for fetuses affected with certain conditions such as Down Syndrome, many feel this inherently devalues the lives of individuals that live with such conditions. These questions are explored in various publications (7-10).

Privacy is critical for genetic testing because of the personal nature of the test results, but it may be practically difficult to achieve. What assurances should be made by laboratories regarding confidentiality? Who owns and controls the data, especially if generated in one lab but refined and analyzed through a multi-part data pipeline? Who should have access to the data? How will patients be protected from improper use? Although the Genetic Information Non-discrimination Act (GINA) prevents the results of genetic tests from impacting access to health insurance and employment, it does not cover life insurance, long-term care, or disability insurance.

Incidental findings

Incidental findings are results that are unintentionally discovered, but may have potential health or reproductive importance. The decision of whether or not to disclose incidental findings requires careful weighing of the benefits against potential risks (11), and

involves evaluating the result's accuracy, significance to health, and clinical actionability (12). Disclosure of incidental findings should be considered if they are life-threatening or if they reveal a medical condition that can be treated or prevented. Incidental findings may occur in clinical laboratories on instruments that perform a set menu of tests, but the tests that can be ordered are a subset of that menu, e.g. blood gas analyzers, multiplex molecular panels, or genomic sequencing assays. Clinical laboratories should have policies to control the performance of tests that may produce incidental findings, and what to do with such findings.

When deciding if a result should be disclosed, persons have both the "right to know" and the "right not to know" (12). In 2013, the Bioethics Commission provided context-specific guidelines for disclosing incidental findings. In their report, they stress that whenever possible, individuals should be informed of the potential for incidental findings before testing, and of how these findings will be handled (11). This allows the individual to have control over disclosure of their results. This is particularly important for genetic testing.

SUMMARY

Even though most clinical laboratorians do not see or treat patients, they must be held accountable to the highest ethical and professional behavior. Recognition and understanding of ethical issues is essential to practice of laboratory medicine. When faced with ethical decisions, laboratorians should seek the input of other clinicians and laboratory colleagues and develop policies to address potential ethically-challenging situations. In addition, most hospitals have ethics boards comprised of multidisciplinary teams of clinicians, lay people and clergy to help guide decision making.

*Note that this article is taken in large part from a recent review article published by the authors and published in *Clinical Chemistry* (*Clinical Chemistry* 2019;65: In Press http://clinchem.aaccjnls.org/cgi/doi/10.1373/clinchem.2019.30667). The reader is referred there for additional detail.

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Excerpts from the Literature

Khushbu Patel, PhD, DABCC, FAAC, Associate Director of Clinical Chemistry, Children's Health. Assistant Professor of Pathology, UT Southwestern Medical Center, Dallas, TX, USA

Ethical Debate surrounding Newborn Genetic Sequencing

Newborn sequencing research has brought about questions that raise both moral and ethical concerns. The ensuing controversy centers around the question: should information regarding adult-onset conditions be disclosed for a newborn if it is not relevant to the patient's current or imminent health?

The question arose from the NIH-funded BabySeq (Genome Sequence-Based Screening for Childhood Risk and Newborn Illness) Project, which aimed to assess the medical and socioeconomic impact of genome sequencing in healthy and sick newborns. The study enrolled a total of 159 infants, with 32 infants from the NICU and the remaining 127 being healthy infants [1,2]. It was a randomized trial where half of the participants were randomly assigned to either standard care (standard newborn screening) or standard care plus genomic sequencing. In the study arm, participants received a report that listed any pathogenic or likely pathogenic variants associated with only childhood-onset diseases.

Five years into the study, a case of a male infant identified with a BRCA2 mutation was reported[3]. The study investigators obtained permission from the institutional review board (IRB) to release the adult-onset findings to the family. The rationale behind disclosing this information to the family was the moral distress endured by the researchers and to "avoid the ethical dilemma of laboratory personnel knowing something that is widely considered to be actionable but cannot be returned"[3]. The protocol was modified to require participants (parents) to receive results for adult-onset conditions. It was viewed that this modified protocol was in the child's best interest, which includes "not only the child's future autonomy to make decision about what the child wants to know about him- or herself, but also having his or her parents alive and well" – the family benefit[3].

Though this seemed to be a logical argument, which was approved by the IRB, ethicists are questioning the concept of family benefit that was raised in this scenario[4]. Of note, it was not detailed whether any benefit was observed from disclosing the findings of the BRCA2 mutation to the parents. The revised study protocol made it mandatory to report adult-onset conditions even though they have no immediate clinical impact on the child's health. As detailed in this current issue's "Ethical Issues in Laboratory Medicine" article, the core principles of medical ethics include respect for autonomy, beneficence and non-maleficence (avoiding harm). In order to breach any of these ethical principles, it requires careful consideration of whether the benefits outweigh the risks and harms[5]. As evidenced by this case, navigating these issues becomes especially delicate when it comes to genetic testing in newborns.

The general consensus recommendation from the pediatrics, ethics and genetics organizations in the United States is that adult-onset-only conditions should not be tested for in children. In doing so, this preserves the autonomy of the child to decide whether to undergo testing for these conditions as an adult and with whom they want to share this information. However, in 2013 the ACMG issued a statement requiring laboratories performing clinical sequencing to report

mutations for select adult-onset conditions in all subjects regardless of age. This list initially comprised of 57 genes and was considered a form of "opportunistic screening"[6]. However, in response to criticism of these new recommendations, the ACMG modified the recommendation in 2014 to allow parents to opt out of opportunistic screening.

These recommendations are well aligned with the ethical principles outlined in the article by Gronowski and colleagues[5]. Patients should at the minimum be given the choice "to know" and "not know" the results of sequencing that are not relevant to the patient's imminent health. This is especially important when dealing with a critically ill newborn, where knowledge of information not directly relevant to the newborns' health can cause additional distress to the parents and family. The strongest case for mandatory disclosure can only be made when findings result in the discovery of conditions that would have immediate measurable health benefits or change clinical management of the patient's condition. Ross and colleagues emphasize that studies should be designed so that they minimize the risk of identifying mutations associated with adult-onset-only conditions. Furthermore, this case also highlights the importance of having a plan and procedure in place to handle incidental findings in the event unexpected information is uncovered.

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Interview with a Distinguished Colleague

By Angela Ferguson, PhD

Uttam Garg, PhD, DABCC, FABT,FAACC

Division Director, Laboratory Medicine Director, Clinical Chemistry, Toxicology, Biochemical Genetics, Children's Mercy. Professor of Pediatric Pathology, University of Missouri-KC School of Medicine, Kansas City, MO

What are some challenges you see currently facing the field of laboratory medicine?

Globally, particularly in the United States, healthcare costs are increasing exponentially and outpacing overall inflation by several fold. Everyone, including outpatient services, hospitals and healthcare providers are expected to deliver more with less. Patients are being asked to dig deeper in their pockets to meet their healthcare expenses. Laboratory medicine is not an exception. Despite increasing costs and complexity of testing, laboratory budgets are being trimmed and reimbursement rates are going down. Providing quality laboratory services at an affordable cost is an ongoing challenge and will likely continue to be so.

Availability of qualified laboratorians is another challenge for the clinical laboratories. Laboratorians are retiring at a faster pace than the number of new graduates entering the workforce. Finding qualified clinical laboratory scientists for specialized areas is even more challenging. For example, finding technologists for areas like toxicology and biochemical genetics is a real challenge. Medical technology programs are not geared towards educating trainees for specialized laboratory services such as mass spectrometry, flow cytometry and molecular testing.

Teaching residents, fellows, and medical staff, particularly in light of a shrinking laboratory medicine curriculum in medical school, is a challenge and opportunity for laboratorians. We should highlight, teach and demonstrate the vital role the clinical laboratory plays in patient care and not let the laboratory services become a commodity.

In addition, laboratorians are being challenged with increasing regulations, particularly for laboratory-developed tests. Laboratorians ought to be innovative to meet these challenges and provide the excellent vital services of laboratory diagnosis.

What changes do you see in the future of pediatric or maternal fetal laboratory medicine?

It is very exciting time for pediatric-maternal laboratory medicine. I think laboratory medicine for this group is changing at the fastest rate. For example, not that long ago we were screening newborns for only a few disorders. Now, in the United States, newborns are screened for over 50 disorders and that number will continue to grow. Laboratories play a vital role in screening and follow-up of these disorders. Sequencing DNA (targeted, exome or whole genome) for improving newborn screening is a hot topic for possible future implementation. It is not uncommon to perform exome or whole genome sequencing on pediatric patients who remain undiagnosed by common laboratory investigations.

Laboratories are going to see increased numbers of “tiny” volume samples from an increasing number of very-low weight newborns. Laboratories will also see increased numbers of new diagnostic biomarkers as our knowledge expands on the pathogenesis of pediatric diseases through genomics and metabolomics. Also, I think we will continue to see increased numbers of new drugs of abuse and toxins in pediatric toxicology.

What development would you like to see occur in pediatric laboratory medicine over the next 3 years?

Despite a number of ongoing efforts in developing pediatric reference intervals and significant progress made, good reference interval data for many analytes, particularly on premature and newborn babies, is still lacking. Pediatric laboratories need continued significant efforts in this area. In an era of big data and machine learning, maybe it is time to think about other innovative ways of generating reference intervals or following a patient with his or her own (intraindividual) values for health and disease.

Pediatric laboratories deal with very small sample volumes. Due to small sample volumes,

an estimated 25-50% of samples are handled manually. No significant progress has been made in automation for handling these samples. Even tubes dead volume has not changed significantly in decades. Development in these areas are definitely needed. Also, I would like to see the use of better technologies, like mass spectrometry for the analysis of certain analytes such as steroid hormones.

Board News!

It is my pleasure to announce the newly elected board members for the Pediatric and Maternal-Fetal Division:

Chair-elect:	Stanley Lo
Secretary:	Mark Kellogg
Treasurer:	Joesph Wiencek
Members at Large:	Van Leung Pineda Laura Smy

Congratulations to the new board members!

Thank you to everyone who ran for a position. There was a fabulous group of candidates, and your interest in the division is greatly appreciated!

Angela Ferguson

Chair, AACC PMF Division

Editor's Note

It has been a pleasure serving as the PMF division newsletter editor for the last 3.5 years. I would like to thank the help and support of the editorial board members during my tenure: Drs. Brenda Suh-Lailam and Kelly Doyle, who are also leaving their positions. I would like to welcome new editorial board members Drs. Khushbu Patel and Stephen Roper. I would also like to welcome our new editor Dr. Sarah Wheeler.

I also want to thank all the members of the PMF board with which I have interacted during this time, and who provided me support and guidance, especially the division chairs: Drs. Shannon Haymond, Alison Woodworth and Angela Ferguson. Finally, I want to thank our readers for your support.

Sincerely,

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2020 PMF Division Executive Board:

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