

ISSUE

13

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2023

Official Newsletter
of the Pennsylvania
Association of
Genetic Counselors

PAGC News

The PAGC Newsletter is brought to you by members of the PAGC Membership Committee

Susan Walther, MS, CGC

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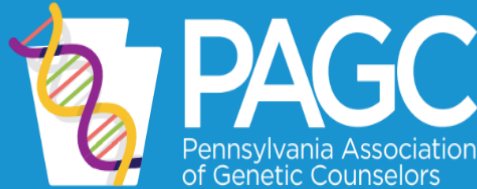
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If you have anything that you would like to share, including upcoming events, seminars, an exciting new career role, etc., please contact us at :
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**PAGC ANNUAL CONFERENCE
SAVE THE DATE
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WELCOME TO OUR NEW PAGC EXECUTIVE BOARD for 1/1/2024 - 12/31/2025:

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PAGC EXECUTIVE BOARD MEMBERS

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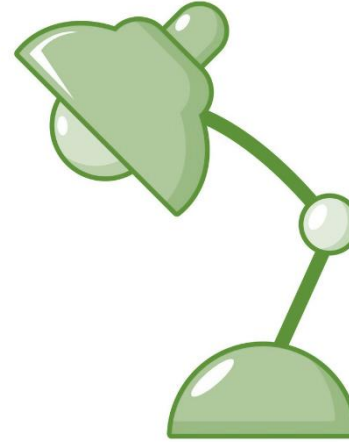
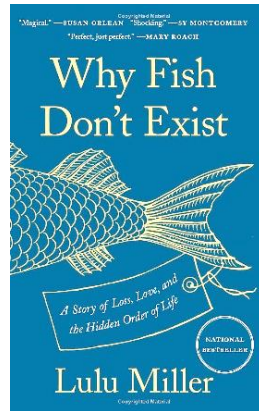
Director-at-Large:

Margaret Harr, MS, CGC

Why Fish Don't Exist

By Lulu Miller

Book Review by Amy Biery Kunz, MS, CGC



Named Best Book of 2020 by *The Washington Post*, "Why Fish Don't Exist" by Lulu Miller is a captivating exploration of identity, science, and the human need to categorize the world around us. Miller takes readers on a journey through the life of David Starr Jordan, a renowned ichthyologist who believed he had discovered the key to classifying all fish species. After the 1906 San Francisco earthquake demolished his life's work by sending thousands of glass jars containing his specimen collection crashing to the floor, Miller details how Jordan rebounded after all seemed lost - reflecting on the nature of existence and the impermanence of labels.

As was the case for many biologists at the start of the 20th century, Jordan's legacy was complicated by eugenic ideologies. Miller reflects on the darker corners of scientific history and the ethical dilemmas that arise when scientific and social agendas become intertwined.

Miller's prose is both poetic and introspective, allowing readers to connect deeply with the personal struggles of not only Jordan but of the author herself. The book invites readers to question the boundaries of knowledge and the impact of hubris within scientific pursuits. In the end, "Why Fish Don't Exist" is a page-turning blend of history, science, and philosophy that invites readers to contemplate the complexities of identity, the fallibility of human categorization, and the ethical implications of scientific discovery.

Featured Genetic Counselor: Anna Raper

Genetic Counseling Program: Arcadia University
Year of graduation: 2016

Current Employer: Penn Medicine



What attracted you to pursue a career in genetic counseling?

Genetic counseling did not exist in my awareness until several years after undergrad. My major combined coursework in psychology and biology, and I interned in a basic neuroscience lab for a year or two. The graduate student I worked with was brilliant and an inspiration – though it was through a part time administrative assistant job in the department of Psychiatry where I got the inkling that a career involving patient interaction would be a better match for me.

Fortunately, I found a position working first as a research assistant and then as a research coordinator on clinical drug trials. These jobs provided valuable training and experience in patient care and communication. I happened to meet two genetic counselors during that time – one through a personal connection, and the other who was supporting a mutual work project. These GCs gave me the introduction to genetic counseling, and I was able to shadow for a couple of their clinics. During my work on the clinical trials, I met several patients with rare hereditary lipid disorders. I was able to see a glimpse of the impact of knowing a specific diagnosis, the potential for targeted therapies, and ability to counsel about familial implications. After that work experience and finding genetic counseling, my goal to pursue a career in the field became very clear.

What are your responsibilities in your current position?

I am in a bit of a transition period! I am a genetic counselor at Penn Medicine, and up to this point have been seeing patients alongside the geneticists in the Adult Medical Genetics clinic. I've worked both in a clinic focused on rare hereditary cancer syndromes (including VHL, tuberous sclerosis complex, neuroendocrine tumor predisposition syndromes) as well as a general adult genetics clinic. For the last 2-3 years, up to half of my time has been dedicated to providing genetic counseling support on research projects. I've been involved in the design of patient and provider educational materials, design of study workflows, and return of research genetic test results.

Currently, I am starting the new Advanced Research Training for Genetic Counselors certificate program at the University of Pennsylvania. For one year, 0.5 FTE will be dedicated to this program, which includes didactic research training, research mentorship and completion of a research project. I am incredibly grateful and excited to be included in the inaugural class of this program!

How have you seen opportunities for genetic counselors evolve during the course of your career?

While I've held a similar position in title since I graduated, even my role at Penn has changed over the years. Our team has grown from two GCs to seven – partly because GC support is being requested in more areas of medicine, and, relevant to my own position, research opportunities for GCs are increasing in number. I'm particularly excited to see more grant funding available for GC-led research. With the education provided by the ART-GC program I hope to pursue those opportunities.

What “I wish I knew then what I know now” advice would you give to recent GC grads?

If there's a particular topic or condition you have a special interest in – dive in! You can become an expert faster than you think, and already know more than you think. It's okay NOT to have all the answers. Be ready to talk about DTC testing on a moment's notice (questions could come from your patients, colleagues, family, taxi driver, IT specialist, anyone!)

HOT TOPIC: Pregnancy and Neonatal Outcomes after Transfer of Mosaic Embryos

Sina Abhari and Jennofer F. Kawwass

Summary by Susan Walther, MS, CGC

J Clin Med. 2021 Apr; 10(7): 1369

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8037456/>

The first application of PGT was reported in 1990 in the UK for selection of XY embryos to prevent X-linked conditions. Preimplantation genetic testing for aneuploidy (**PGT-A**) of embryos during in vitro fertilization (IVF) has grown increasingly common; transfer of a euploid embryo is associated with an increased likelihood of implantation and a decreased miscarriage risk. The major factor leading to the failure of an embryo to result in a pregnancy is aneuploidy. Most aneuploidies arise from maternal meiosis, and they increase exponentially in women over the age of 35 years. Research studies have shown that the incidence of aneuploidy increases from 30–50% in patients under 35 years of age to 80% in women 42 years of age or older.

Although some studies have shown improved clinical outcomes with PGT-A, specifically in women with advanced maternal age, the value of PGT-A as a universal screening test for all IVF patients is yet to be determined. Another potential benefit of PGT-A is the opportunity to reduce maternal and neonatal morbidity secondary to multiple gestations by allowing the transfer of fewer embryos while maintaining success rates.

At the blastocyst stage, embryos undergo the first cellular differentiation, forming the outer trophectoderm (**TE**) and an inner cell mass (**ICM**). The TE will form the placenta, whereas the ICM will form the embryo. The development of new diagnostic techniques for PGT-A, such as next-generation sequencing (NGS), has led to increased reporting of embryonic mosaicism. It is important to emphasize that in contrast to meiotically derived aneuploidy, mosaicism arises through mitotic malsegregation after fertilization and increases with cleavage-stage dysmorphism, but not with advancing maternal age. The rate of embryonic mosaicism may vary based on a number of factors, including the stage of the embryo at the time of biopsy as well as the chromosomal detection technique used. Advanced techniques used to assess the copy number of all 24 chromosomes from a single or multiple cell biopsy report ~20–30% mosaicism of blastocyst-stage embryos across all maternal ages. Given that a mosaic result may not necessarily represent the chromosomal constitution of the remainder of the embryo, embryos diagnosed as mosaic based on trophectoderm (TE) analysis may be fully euploid, fully aneuploid, mosaic for a euploid and an aneuploid cell line, or mosaic for two or more different abnormal cell lines.

The American Society for Reproductive Medicine (ASRM), the Preimplantation Genetic Diagnosis International Society (PGDIS), and Congress on Controversies in Preconception, Preimplantation and Prenatal Genetic Diagnosis (CoGen) have issued similar statements with recommendations for clinical management of mosaic embryos. When no euploid embryos are available for transfer and both the clinician and patient are comfortable with transfer of a mosaic embryo, guidance exists regarding the prioritization of embryos. Based on current evidence, clinicians are encouraged to prioritize mosaic embryos with low-level mosaicism over high level mosaicism for transfer. In cases of single chromosome mosaicism, embryos mosaic for chromosomes with a known potential for IUGR (chromosomes 2, 7, 16), live born syndromes (chromosomes 13, 18, 21) or UPD should be avoided.

Existing data regarding neonatal outcomes after mosaic embryo transfer (**MET**) are somewhat reassuring, with live birth rates ranging from 30% to 48% and miscarriage rates ranging from 20% to 33% per mosaic embryo transfer. However, many questions remain unanswered such as the reliability of prenatal screening methods, including cell-free fetal DNA tests (NIPT), risk of congenital abnormalities, and long-term outcomes of infants born after MET. Most experts agree that transfer of mosaic embryos should only be considered in situations in which no euploid embryos are available for transfer and after comprehensive genetic counseling with an emphasis on prenatal diagnostic testing. CVS might be limited to follow-up on PGT results, particularly mosaic results because the placenta stems from the trophectoderm. Amniocentesis should be considered if information is desired on whether the fetus is actually affected. Alternative options, including third party reproduction, should be presented to couples. Future studies that focus on perinatal and long-term outcomes of children born after transfer of mosaic embryos may help elucidate the potential long-term implications of MET.

Featured Genetic Counselor: Kelly Morgan

Genetic Counseling Program: Icahn School of Medicine at Mount Sinai
Year of graduation: 2017

Current Employer: Geisinger Medical Center



What attracted you to pursue a career in genetic counseling?

I first learned about genetic counseling from an unexpected source – my high school math teacher. He shared that his wife was a genetic counselor and encouraged me to consider this career based on my interest in the genetics unit of my biology class. Subsequent experiences learning more about the field through shadowing opportunities, conversations with a college guidance counselor, and reading (I loved the book “Telling Genes: The Story of Genetic Counseling in America”), confirmed that the field of genetic counseling was a fascinating combination of human connection and cutting-edge science. I completed a B.S. in Genetics at the University of Wisconsin-Madison and gratefully accepted a spot in Mount Sinai’s genetic counseling program following graduation.

What are your responsibilities in your current position?

I work as a research genetic counselor at Geisinger. My responsibilities include: Disclosing clinically actionable genetic variants to patients enrolled in a hospital wide biobank through the MyCode® Genomic Screening and Counseling program; being a member of a multi-disciplinary team investigating novel strategies to improve cascade testing uptake in families with Familial Hypercholesterolemia; (strategies include a patient and provider facing packet, a chatbot, and a direct contact program); applying qualitative research methodologies, implementation science, and health communication science to better understand patient experiences and develop new modalities to support patients throughout the continuum of their care (strategies include user-testing of a pre-visit chatbot developed to prime patients for their upcoming appointment and provide genetic counselors with information on how patients are coping with their results and Photovoice interviews – photos from patients are discussed through semi-structured interviews to delve into their experience with Familial Hypercholesterolemia, Hereditary Breast and Ovarian Cancer syndrome, Lynch syndrome, or Cardiomyopathy). My role at Geisinger has highlighted the range of opportunities within research that genetic counselors can pursue.

How have you seen opportunities for genetic counselors evolve during the course of your career?

As an early-ish career genetic counselor, I am particularly excited about how much the field has changed during my time in this profession. One area that I feel illustrates this well and has been a professionally rewarding throughline for me is population screening. I recall Dr. Mary-Claire King speaking at my first NSGC conference in 2016 imploring the field to consider population screening for *BRCA1/2*. In my first role at Memorial Sloan Kettering Cancer Center, I remember the excitement in rolling out a novel research program to offer population screening for the *BRCA1/2* Ashkenazi Jewish founder variants in early 2018. Thinking about my current position which involves returning likely pathogenic and pathogenic variants in over 80 clinically actionable genes to an unselected population, I am amazed at how much has changed in the last 7 years. This evolution provides opportunities for genetic counselors to explore new ways to continue to support patients from the point of access to genetic testing through longitudinal follow-up care.

What “I wish I knew then what I know now” advice would you give to recent GC grads?

I think it is important to be thoughtful in how you pace yourself throughout your career. As a recent graduate (and even sometimes now), I felt the need to say yes to every professional opportunity. I believe that finding a mix of personally and professionally fulfilling activities is key to continuing to be professionally productive.

HOT TOPIC: Gene Therapy for Duchenne Muscular Dystrophy

Summary by Kelsey Bohnert, MS, CGC

On June 22, 2023, the FDA approved, **Elevidys**, the first gene therapy for *DMD*-related muscular dystrophy, after an expedited review. This accelerated approval was the outcome of decades of work by advocacy organizations, individual, and families impacted by the disease, healthcare providers, researchers, and the immense backing from Sarepta, the company that developed the biologic. While this news certainly signals a new era in *DMD* treatment and will impact the lives of many patients and families living with Duchenne Muscular Dystrophy, caution should be exercised before introducing this as a magic cure.

DMD-related muscular dystrophy is an X-linked disease caused by specific pathogenic variants in the *DMD* gene. More broadly, genetic variants in the *DMD* gene cause dystrophinopathies, which represent a spectrum of disorders from asymptomatic increase of CPK to muscle cramping to dilated cardiomyopathy and involvement of the skeletal muscle, as is the case with Duchenne and Becker muscular dystrophies (*DMD* and *BMD*). The NIH GeneReviews [article](#) offers a comprehensive review of the clinical presentation and differentiation of these diagnoses. Elevidys, as well as other genetic-based therapies, focus on the treatment of the more severe disease presentation and have variant-specific inclusion and exclusion criteria.

The *DMD* gene is the largest in the human body, with 79 exons. The exons code for dystrophin, which is part of a larger group of proteins that strengthen muscle fibers and protect them from injury during use. If dystrophin is not present, muscles break down over time, which can be measured in the elevated CPK. Eventually, muscle tissue is replaced with fat. The amount of dystrophin dictates the severity of the disease, which is informed by the specific genetic variant. If a variant is “in-frame,” the reading frame is not disrupted, and some dystrophin can be preserved. An “out-of-frame” variant would result in no dystrophin. In severe cases, developmental delay and muscle weakness are often noted by 3 years of age, but elevated CPK is noted from birth.

More than 5,000 pathogenic variants have been identified and can include whole gene deletion, deletion or duplication of one or more exons, or single base changes. Exon-based deletions account for the majority of pathogenic variants (60-70%) and have been the focus of initial *DMD* treatments, called exon skipping therapy. By considering the patient’s deletion and “skipping” to an adjacent exon, the reading frame is restored and, ideally, results in a residual protein product. The FDA has approved four **exon skipping therapies—Amondys 45, Exondys 51, Viltepso, and Vyondys 53**. These therapies were also approved under the accelerated pathway based on early data showing an increase in dystrophin production.

The impact of these treatments must be considered in the context of the vastness of the *DMD* gene. As the names suggest, their use is for patients with deletions amenable to skipping of exons 45, 51, or 53. Together this accounts for 29% of those impacted with *DMD*. Other treatments have focused on other changes, like Ataluren, that focus on protein restoration of nonsense mutations. Ataluren is approved in Europe and some other countries, but has not earned FDA approval in the U.S. Development of other therapies are underway, some of which have reached clinical trials. Examples includes exon 44 skipping, use of approved therapies for patients with duplications rather than deletions in a subset, new formulations of exon 53 skipping, and consideration of combining exon skipping therapies.

These treatments are extremely variant-specific and must be administered weekly via hour-long IV infusions at a specialized center. With only a subset of patients being eligible, and the results being variable and short-lived, gene therapy has been extremely sought after for long-term benefit. Rather than ongoing treatments to slow down the progression of symptoms in variant-specific populations, gene therapy could offer a more universal approach to correct the consequences of genetic errors.

Elevidys is designed to deliver a micro dystrophin protein using a viral vector, AAVrh74. An ideal vector is designed to target affected cells—in this case skeletal muscle—and to minimize an immune response. While AAVrh74 may not create symptoms on its own, a patient may have encountered it in their daily lives, so a screen for antibodies is completed prior to drug administration to guard against an adverse reaction. This one-time dose is given intravenously.

CONTINUED ON PAGE 7

Because the drug targets muscle tissue and is then processed by the liver, side effects and ongoing monitoring focus on liver health, GI-related concerns, and inflammation of muscles, including those in the heart. The drug has been approved for 4–5-year-olds who are still ambulatory with a confirmed genetic variant in the *DMD* gene. Approval requires negative AAVrh74 titers and standard dose of corticosteroids leading up to treatment. Elevidys is contraindicated for individuals with deletions involving exons 8 or 9 due to observed immune-mediated myositis requiring hospitalization. Clinical trials focused on patients with genetic variation in exons 18-58 and after 71, so those with mutations in exons 1-17 and 59-71 may be at an increased risk of a severe immune-mediated myositis reaction.

These recommendations are based on the results of a clinical trial that followed 41 patients, ages 4-7, over two 48-week periods. The first part was a double-blind, placebo-controlled period, and the second part began immediately after the first where the groups were switched so that ultimately each group had 48 weeks receiving the placebo and 48 weeks receiving Elevidys. The goal of this trial was to determine the expression of the micro dystrophin in skeletal muscle via western blot on muscle biopsy, and difference on the North Star Ambulatory Assessment (NSAA)—a gold standard in describing the course of *DMD*-related disease. Results of the study showed an increase of expression micro dystrophin over the course of the 48-week treatment period and improvements on the NSAA for patients 4-5 for those who received Elevidys. The NSAA scores decreased for the age 6-7 cohort, though neither group's change was statistically significant. A second study is underway with 20 more patients, again ages 4-7, with frameshift, splice site mutations, or premature stop codon mutations. Future studies will consider effectiveness in a wider range of patients, such as broader age ranges and ambulatory status. Sarepta is the first company to obtain approval for *DMD* gene therapy, but other companies, like Pfizer, are considering other vectors, promoters and trans gene technology.

While Elevidys has been approved by the FDA, it will still be many months before it reaches hospitals to begin treatment. Before patients can benefit from its use, healthcare providers must navigate insurance approval, and hospitals must create protocols for storing and administering the biologic. Luckily, many care centers have navigated this process with the SMA gene therapy, Zolgensma, so there is hope that protocols are already in place. Most care centers have already reviewed their patient populations and have had conversations with their eligible patients, including those who may be turning 4 years old in the next few months. There have also been difficult conversations with families who had declined exon-skipping therapy to be eligible for the gene therapy, but whose children now do not meet the narrow eligibility criteria, mostly due to age and ambulatory status.

In the last decade, patients, families, and healthcare providers have seen tremendous strides in the management of *DMD*-related muscular dystrophy, and with it an increase in life expectancy and quality of life. In addition to the explosion of treatments from Exondys 51's FDA approval in 2016, to Elevidys's approval this summer, there are more tools than ever to combat the most common causes of congenital myopathy. A recent meta-analysis by Brookfield et al., found the average life expectancy of someone with *DMD* to be 22 years old; however, this expectancy has substantially increased for those born after 1990 to 28.1 years, with more patients now living into their 30s and beyond, even with earlier age of onset (2021). While some of this improvement can be due to these novel therapies, credit is also due to increased standards of care. The advocacy organization **Parent Project Muscular Dystrophy** worked with a multidisciplinary team of experts to publish 3-part articles that outlined best practices for all members of the care team—from neuromuscular to bone health, to primary care and emergency management. With the emergence of gene therapy, some patients and families may be disappointed by not qualifying for a treatment they thought to be universal. Though Elevidys gene therapy may not be what was expected, it is a pivotal next step in *DMD* care and serves as another reminder that multidisciplinary care for patients with complex diseases is paramount.

VISIT THE PAGC WEBSITE FOR DUCHENNE MUSCULAR DYSTROPHY RESOURCES

(www.pennsylvaniagc.org)



PAGC Committees

Volunteers are always welcome!

Contact committee chair if you are interested in being involved

Education

Chairs:

Shannon Terek (terks1@chop.edu)

Lucy Galea (lucygalea@gmail.com)



Planning for the annual conference is underway for speakers, events, sponsors, and vendors. Please contact the committee chairs with suggestions or to be involved in the planning, abstract review, or volunteering for on-site logistics.

***SAVE THE DATES: Annual Conference
March 21-22, 2024 at Magee Women's Hospital, Pittsburgh***

Professional Issues

Chair: Becky Belles (rsbelles@geisinger.edu)



- Work to update GC licensure in PA
- Examine barriers to credentialing of GCs in PA
- Create awareness of healthcare bills being considered in PA legislature

Genetic Services

Chair: Gabby Shermanski (gtshermanski@geisinger.edu)

- Design and implement Pennsylvania Professional Status Survey
- Evaluate and promote GC services in PA
- Create social media content



Membership

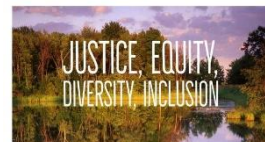
Chair: Susan Walther (susanwalther1203@gmail.com)



- Maintain PAGC website content
- Create e-blast communications
- Manage registration for annual conference
- Develop articles for PAGC newsletter

Justice, Equity, Diversity and Inclusion

Chairs: Kelsey Bohnert (kelsey.bohnert@chp.edu) and Aaron Baldwin (aaron.baldwin@penmedicine.upenn.edu)



This committee will be working on developing a recorded webinar series, as well as partnering with high schools and genetic counseling programs to increase high school students' exposure to the field of genetic counseling through the creation of a toolkit. Please contact the committee chairs for more information or to express your interest in joining the committee.