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PGDIS CONFERENCE

PREIMPLANTATION GENETIC DIAGNOSIS INTERNATIONAL SOCIETY

PGDIS

6-8 May 2024
Kuala Lumpur
Malaysia

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Heterozygote Status as Health Risk: Changing the Role of Carrier Screening in Preconception Care and How Couples and Individuals Should Be Counseled About Results

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What is the point of carrier screening?

"To facilitate reproductive choices for those found to be at high risk for having a **child with a serious genetic disease**"

1. Education
2. Pregnancy termination
3. Preimplantation genetic diagnosis
4. Possible treatments (one day….)
5. Regardless of ancestry: increases equity and reduces stigmatization
6. Should optimally be done preconceptionally

European Society of Human Genetics. Henneman, et al. *European Journal of Human Genetics* (2016)

Facts

- More than **1,300** recessively-inherited genetic disorders
- Affecting 30/10,000 children
- Mendelian disorders account for ~20% of infant mortality
- Genetic disease is the single most common cause of hospitalizations in pediatric hospitals

Expanded Carrier Screening

- Expanded carrier screening provides improved detection of carrier couples than screening based on racial/ethnic criteria
- Such screening is optimally performed prior to pregnancy, when such information can be used to guide management that can profoundly reduce the likelihood of an affected child
- Counseling prior to and after screening will improve the process and empower women and couples to obtain the information that they seek

But...

Carrier Screening

- **The increasing election of carrier screening, along with decades of experience in providing carrier screening to couples and individuals seeking to conceive, has now called into question the assumption that being a carrier for most autosomal or X-linked recessive conditions (heterozygote) conveys little to no clinically relevant risk for disease development.**

Why the change?

Carrier Screening

- The development and implementation of carrier screening was focused on the identification of single-gene disorders that were associated with adverse **pediatric** phenotypes.
- Such phenotypes were associated with a biallelic presence of pathogenic variants in autosomal recessive genes and a monoallelic X-linked pathogenic variant in males with X-linked recessive conditions.
- In the vast majority of such conditions, carriers of pathogenic variants were not characterized by the severe phenotype, lest they be classified as a dominant condition, and all were clearly able to reproduce as evidenced by their participation in carrier screening programs.

Changes in Carrier Screening

- Expanded number of genes historically associated with autosomal recessive and X-linked monogenic conditions are now readily available for assessment in easy-to-access panels
- Considerable amount of time (decades in some cases) has elapsed whereby a clinical correlation could now be considered in associating the development of adult-onset conditions with heterozygote status.
- Improved ability to correlate medical records of individuals who develop diseases/conditions with earlier genetic testing results (AI???)

The “Healthy” Heterozygote

- Gregor Mendel’s foundational pea plant experiments and their outcomes used to characterize disease expression, first put forth by Archibald Garrod in his discovery of Alkaptonuria in 1902.
- According to Mendelian inheritance, if a genetic trait is recessive, the offspring of a “cross” need to inherit two copies of the variant-containing gene for the trait to be expressed at an organic level.
- Otherwise, they will exhibit only the other, dominating trait from the “wild-type” allele as the resultant phenotype.
- Thus, according to the well-established concept that has become dogma, recessive alleles are masked by dominant alleles after a successful mating.

Farrell et al 2021

The “Not-So-Healthy” Heterozygote

- Being heterozygous generally implies having 50% or the normal expression for an autosomal recessive gene. If having 50% activity causes a disease phenotype, then the variant is considered dominant; if not, then it is termed recessive.
- However, under some circumstances, the threshold could be less and result in the appearance of symptoms, particularly if stressors create greater susceptibility to cause an additional deficit of the essential metabolic function involved or other genomic factors impact gene expression.
- We thus recognize that stressful circumstances or unique genomic phenomena can potentially unmask a recessive variant when the disease, even in mild form, presents in heterozygosity.

Farrell et al 2021

The “Not-So-Healthy” Heterozygote

- An increasing number of case reports have suggested that mild and nonspecific symptoms can occur in some heterozygotes, as symptomatic heterozygotes have been identified across different disease types, including neurological, neuromuscular, hematological, and pulmonary diseases.
- The symptoms reported in such individuals are invariably milder in heterozygotes than in biallelic variants and usually occur “later in life.” The status of symptomatic heterozygotes as separate entities is often disputed, and alternative diagnoses are frequently considered.
- Indeed, often only a “thin line” exists between dual, dominant, and recessive modes of inheritance and symptomatic heterozygosity.
- Interestingly, recent population studies have found global disease effects in heterozygous carriers of some genetic variants.

Kalyta et al 2023

The “Not-So-Healthy” Heterozygote: Self-Inflicted?

- Another consideration is that in our desire to accurately characterize genetic conditions, a rigid classification system emerged that allowed us to predict outcomes and counsel individuals and couples about disease state (i.e., pediatric) and recurrence risks. This rigid classification was based, in no small part, on the original Mendelian experiments and early observation.
- However, that observation, along with increasing understanding of genetic mechanisms of disease, has now brought us to a new concept for carrier screening; that is, for an increasing number of historically biallelic genetic conditions, heterozygote status can carry with it morbidity related to the pathogenic variant.

The “Not-So-Healthy” Heterozygote

- The molecular basis of this phenomenon is still unknown. Possible explanations include:
  - undiscovered deep-splicing variants
  - genetic and environmental modifiers
  - digenic/oligogenic inheritance
  - skewed methylation patterns
  - mutational burden.
- Symptomatic heterozygotes are rarely reported in the literature, mainly because most did not undergo a complete diagnostic process, so alternative diagnoses could not be conclusively excluded.
- However, despite the increasing accessibility to high-throughput technologies, there still seems to be a small group of patients with mild symptoms and just a single pathogenic variant in conditions usually associated with biallelic conditions.

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The “Not-So-Healthy” Heterozygote: Phenotypic Presentations

- Dosage Effect
- Variant Effect
- Novel Phenotype

The “Not-So-Healthy” Heterozygote: Well-Recognized Conditions

- Sickle Cell Disease
- Cystic Fibrosis
- Fragile X

Sickle Cell Disease

- Sickle cell disease refers to a group of autosomal recessive genetic disorders characterized by the presence of two hemoglobin-S (HbS) variants of the β-globin gene or a compound heterozygous combination such as HbS accompanying the hemoglobin-C variant or with the β-thalassemia variant.
- These molecular abnormalities cause erythrocytes to change from their characteristic disc shape to an irregular “sickled” structure that tends to adhere to vascular endothelium and may cause obstructed blood flow and local hypoxia. Sickled erythrocytes are intrinsically unstable and prone to hemolyze, thus causing chronic anemia.
- However, the morbidity of SCD is due primarily to the intermittently obstructed blood flow that can cause severe musculoskeletal pain, strokes, and dysfunction of several organs such as the heart, spleen and kidney. In addition, those with SCD are susceptible to severe bacterial infections.
- The ultimate consequence is reduced life expectancy.

Farrell et al 2021

Sickle Cell Trait (SCT)

- Concerns about health risks in individuals with SCT have been reported for decades, but more recent publications substantiate the potential risks of SCT, particularly chronic kidney disease and pulmonary embolism.
- A 2019 meta-analysis confirmed that SCT increases risk to develop one or more SCD symptoms, including
  - chronic kidney disease, proteinuria, venous thromboembolism, hyposthenuria, and renal medullary carcinoma
- A perceived risk for exertion-related sudden death in military recruits and collegiate athletes with SCT.

Farrell et al 2021

Cystic Fibrosis (CF)

- Cystic fibrosis (CF) is a common life-threatening genetic disorder with pleiotropic manifestations. It causes excessive salt loss in sweat, chronic and progressive obstructive lung disease, sinusitis, intestinal malabsorption in most patients due to pancreatic exocrine insufficiency leading to malnutrition, liver disease (biliary cirrhosis) in some, and male infertility.
- In North America and western Europe, CF occurs in approximately one of every 4000 births. Of the approximately 30,000 CF patients who live in the USA, 80% of patients are white, but increasingly the disease is being diagnosed in non-white people. CF results from deleterious genetic variants in the cystic fibrosis transmembrane conductance regulator gene (CFTR) located on chromosome 7q31.2, which codes for the CFTR protein.
- Defects in this protein lead to absent or malfunctioning ion channels transporting chloride and bicarbonate in the apical membranes of affected epithelia.

Farrell et al 2021

Cystic Fibrosis (CF)

- CF has always been classified as an autosomal recessive disorder, with individuals who exhibit the CF phenotype have inherited two deleterious variants of the *CFTR* gene.
- Although there are more than 2,000 different *CFTR* variants reported, about 20% of these are well-defined as CF-causing. The most common CF-causing variant, which led to the discovery of the *CFTR* gene, is p.Phe508del
- In North America and western Europe, nearly half of individuals with CF are homozygous for p.Phe508del, an additional 40% have one p.Phe508del allele and up to 15% have two variants other than p.Phe508del
- Thus, the relatively high incidence of CF among autosomal recessive diseases is mostly due to the p.Phe508del allele.

Farrell et al 2021

CFTR-related Conditions

- Biochemical results reported from studies evaluating biochemical and physiological aspects of *CFTR* functioning are consistent and reveal abnormal CFTR functioning in CF heterozygotes, initially described in 1962 by Sant'Agnese and Powell in their study of 97 “obligate” CF carriers and 117 “unselected adult controls.”
- Clinical correlation of these biochemical perturbations include an increased risk for the conditions amongst heterozygotes
  - Pancreatitis
  - Bronchiectasis
  - Congenital bilateral absence of the vas deferens (CBAVD)
  - Asthma

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Fragile X Syndrome (FXS)

Fragile X mental retardation type 1 (*FMR1*) gene premutation is associated with:

- Primary ovarian failure (Fragile X-associated primary ovarian insufficiency [FXPOI])
- Ataxia (Fragile X-associated tremor/ataxia syndrome [FXTAS])
- Additional phenotypes reported include
  - Fibromyalgia
  - Hypothyroidism
  - migraine headaches
  - sleep disturbances
  - sleep apnea
  - restless legs syndrome
  - central pain syndrome
  - Neuropathy
  - neuropsychiatric alterations

Mila et al 2018

ADDITONAL RISK GENES

ABCC8-related familial hyperinsulinism (ABCC8)	Dosage Effect	Diabetes
Adrenoleukodystrophy, X-linked (ABCD1)	Dosage Effect	Approximately 20% of female carriers develop problems resembling adrenomyeloneuropathy; some female carriers have symptoms that typically present later in life than males and rarely develop adrenocortical insufficiency or cerebral adrenoleukodystrophy
Medium chain acyl-CoA dehydrogenase deficiency (ACADM)	Dosage Effect	Female carriers who are pregnant with an affected fetus are at risk for developing AFLP and HELLP syndrome
Polygladular autoimmune syndrome type 1 (AIRE)	Dosage/Variant Effect	Specific mutations (G228W, V301M, and C311Y) associated with AD disease
Hypophosphatasia, autosomal recessive (ALPL)	Dosage/Variant Effect	Mild forms of hypophosphatasia with certain variants
Ataxia-telangiectasia (ATM)	Novel Phenotype	Carriers have an increased risk of developing cancers, including breast, pancreatic, and prostate.

ADDITONAL RISK GENES

ATP7A-related disorders (ATP7A)	Dosage Effect	Some symptomatic females
Biotinidase deficiency (BTD)	Dosage/Variant Effect	D444H mild variant; homozygotes not expected to experience symptoms
Calpainopathy (CAPN3)	Dosage/Variant Effect	Some variants associated with limb girdle muscular dystrophy type 4, which is inherited in an autosomal dominant manner.
Cystic fibrosis (CFTR)	Dosage/Variant Effect	Carriers have an increased risk (less than 1%) for chronic pancreatitis; variants have variable impact on phenotype
Congenital myasthenic syndrome (CHRNE)	Dosage Effect	Rarely, this condition is inherited in an autosomal dominant pattern, in which carriers may experience symptoms.

ADDITONAL RISK GENES

COL4A3-related Alport syndrome (COL4A3)	Dosage/Variant Effect and Novel Phenotype	Some carriers may have isolated, non-progressive blood in the urine (hematuria) (also called benign familial hematuria), while other affected individuals may have more progressive symptoms and develop kidney disease later in life (after age 40).
COL4A4-related Alport syndrome (COL4A4)	Dosage/Variant Effect and Novel Phenotype	Some carriers may have isolated, non-progressive blood in the urine (hematuria) (also called benign familial hematuria), while other affected individuals may have more progressive symptoms and develop kidney disease later in life (after age 40).
COL4A5-related Alport syndrome (COL4A5)	Dosage/Variant Effect and Novel Phenotype	Most female carriers experience hematuria. Later in life, some carriers may also develop other symptoms related to this condition, including varying degrees of hearing loss and kidney failure.
Dystrophic epidermolysis bullosa (COL7A1)	Dosage/Variant Effect	Certain variants are associated with autosomal dominant dystrophic epidermolysis bullosa
Carnitine palmitoyltransferase 1A deficiency (CPT1A)	Dosage/Variant Effect and Novel Phenotype	Female carriers who are pregnant with an affected fetus are at risk of developing acute fatty liver of pregnancy (AFLP).
Chronic granulomatous disease (CYBB)	Dosage Effect and Novel Phenotype	Female carriers rarely have mild symptoms, such as an increased frequency of bacterial and fungal infections (Genetics Home Reference), discoid lupus erythematous (severe rash that gets worse in sunlight), and aphthous ulcers (canker sores)

ADDITONAL RISK GENES

Aldosterone synthase deficiency (CYP11B1)	Variant Effect	Certain gene fusions with CYP11B1 may cause AD aldosteronism
Aromatase deficiency (CYP19A1)	Dosage/Stress Effect	Female carriers who are pregnant with an affected fetus may experience mild symptoms of the disorder that go away soon after delivery.
DHDDS-related disorders (DHDDS)	Variant Effect and Novel Phenotype	Certain variants are associated with developmental epileptic encephalopathy, which is inherited in an autosomal dominant manner.
Dystrophic epidermolysis bullosa (COL7A1)	Dosage/Variant Effect	Certain variants are associated with autosomal dominant dystrophic epidermolysis bullosa
Dystrophinopathy (including Duchenne/Becker muscular dystrophy) (DMD)	Dosage/Variant Effect and Novel Phenotype	Some female carriers may have symptoms, including muscle weakness and cramping, and increased risk of developing DCM
DUOX2-related conditions (DUOX2)	Dosage Effect and Novel Phenotype	One such DUOX2-related conditions includes partial iodide organification defect (PIOD). This is characterized by the impaired ability of the thyroid gland to produce thyroid hormone.

ADDITONAL RISK GENES

Hypohidrotic ectodermal dysplasia, EDA-related (EDA)	Variant Effect	Some female carriers may have mild symptoms, including missing or abnormal teeth, spare hair, and sweat gland function problems; female carriers are at risk for hyperthermia during pregnancy
Emery-Dreifuss muscular dystrophy, EMD-related (EMD)	Dosage Effect	Female carriers are at risk for developing heart problems or mild progressive muscle weakness.
EVC2-related Ellis-van Creveld syndrome (EVC2)	Variant Effect and Novel Phenotype	Certain variants are associated with Weyers acrofacial dysostosis
Factor IX thrombophilia (hemophilia B) (F9)	Dosage Effect	Female carriers may have half, or less than half, the normal amount of coagulation factor IX and therefore, may experience clotting difficulties.
Fumarate hydratase deficiency (FH)	Novel Phenotype	Carriers have an increased risk of developing hereditary leiomyomatosis and renal cell cancer (HLRCC).
Fragile X syndrome (FMR1)	Dosage Effect and Novel Phenotype	Fragile X-associated tremor/ataxia syndrome (FXTAS) and premature ovarian failure (POF)

ADDITONAL RISK GENES

Galactosemia (GALT)	Variant Effect	GALT c.-119_-116del (Duarte variant – mild)
Gaucher disease (GBA)	Novel Phenotype	Carriers are at increased risk after the age of 50 of developing neurologic symptoms consistent with a movement disorder (Parkinson disease or Lewy body dementia).
GJB2-related DFNB1 nonsyndromic hearing loss and deafness (GJB2)	Variant Effect	Certain variants are associated with autosomal dominant non-syndromic (DFNA3) or syndromic (e.g. KID, HID, Vohwinkel) hearing loss and deafness conditions.
Fabry disease (alpha-galactosidase A deficiency) (GLA)	Dosage Effect and Novel Phenotype	Female carriers may develop classic features of the disorder, including nervous system abnormalities, kidney problems, chronic pain, and fatigue. They also have an increased risk of developing high blood pressure, heart disease, stroke, and kidney failure.
Inclusion body myopathy 2 (GNE)	Variant Effect	Certain variants are associated with sialuria, which is inherited in an autosomal dominant manner.
HADHA-related disorders (HADHA)	Dosage/Variant Effect	Female carriers (particularly Glu474Gln mutation – Genetics Home Reference) who are pregnant with an affected fetus are at risk of developing acute fatty liver of pregnancy

ADDITONAL RISK GENES

Alpha-thalassemia triplication (HBA1/HBA2)	Dosage/Variant Effect	Carriers of alpha-thal triplication and beta-thal mutation may be at risk of beta-thal intermedia phenotype
HBB-related hemoglobinopathies (HBB)	Variant Effect	Studies have shown that individuals that are carriers of a harmful genetic change in HBB may be at risk for beta thalassemia intermedia if they are also carriers of one or more extra copies of the alpha globin gene
Mucopolysaccharidosis, type II (IDS)	Dosage Effect	Some female carriers may develop mild symptoms.
X-linked severe combined immunodeficiency (IL2RG)	Dosage/Stress Effect	Female carriers rarely experience symptoms
KCNJ11-related familial hyperinsulinism (KCNJ11)	Dosage Effect	Focal FHI
Herlitz junctional epidermolysis bullosa, LAMB3-related (LAMB3)	Dosage/Variant Effect	Carriers may develop mild phenotype; certain variants are associated with amelogenesis imperfecta, which is inherited in an autosomal dominant manner.

ADDITONAL RISK GENES

Familial hypercholesterolemia (LDLR)	Dosage Effect	Carriers have elevated cholesterol levels that increase risk for cardiovascular disease, most commonly coronary artery disease.
Lipoprotein lipase deficiency (LPL)	Dosage Effect	Carriers are at increased risk of developing cardiovascular disease or diabetes.
Congenital amegakaryocytic thrombocytopenia (MPL)	Variant Effect	Certain variants are associated with essential thrombocythemia, inherited in an autosomal dominant manner.
MYO7A-related disorders (MYO7A)	Variant Effect	Certain variants are associated with autosomal dominant nonsyndromic hearing loss (DFNA11) or autosomal recessive nonsyndromic hearing loss (DFNB2).
Nijmegen breakage syndrome (NBN)	Novel Phenotype	Carriers are at increased risk for breast and other cancers
Steroid-resistant nephrotic syndrome (NPHS2)	Variant Effect	R229Q variant not disease-causing if in homozygous state.

ADDITONAL RISK GENES

Retinitis pigmentosa 37 (NR2E3)	Variant Effect	Certain variants are associated with autosomal dominant retinitis pigmentosa, and there is evidence suggesting that NR2E3 variants are also associated with autosomal recessive RP
Costeff optic atrophy syndrome (OPA3)	Variant Effect	Autosomal dominant optic atrophy and cataract. Onset can occur from infancy to adulthood.
Ornithine transcarbamylase deficiency (OTC)	Dosage/Stress Effect	Approximately 15-20% of female carriers may develop mild symptoms of the condition
Pyruvate dehydrogenase deficiency PDHA1-related, (PDHA1)	Dosage Effect	Many female carriers have symptoms that range from mild to similar to those in affected males.
Peroxisome biogenesis disorder, type 4 (PEX6)	Variant Effect	Only one variant known at this time with AD inheritance.
PRPS1-related disorders (PRPS1)	Dosage Effect	Some female carriers may have symptoms, such as hearing impairment or mild nerve damage.

ADDITONAL RISK GENES

X-linked juvenile retinoschisis (RS1)	Dosage Effect	Female carriers may have flecks or other signs on their retinas that do not cause any health problems.
RTEL1-related disorders (RTEL1)	Dosage Effect	Recent studies have shown that carriers of RTEL1-related disorders may be at risk of developing familial interstitial pneumonia, idiopathic pulmonary fibrosis, myelodysplastic syndrome, or other symptoms at older ages.
Alpha-sarcoglycanopathy (including limb-girdle muscular dystrophy, type 2D) (SGCA)	Dosage Effect	Carriers may develop mild phenotype
Delta-sarcoglycanopathy (SGCD)	Dosage Effect and Novel Phenotype	Carriers may be at risk for dilated cardiomyopathy.
Sulfate transporter-related osteochondrodysplasia (SLC26A2)	Novel Phenotype	Fetuses with achondrogenesis type 1B are often breech and mothers are prone to other pregnancy complications.
X-linked creatine transporter deficiency (SLC6A8)	Dosage Effect and Novel Phenotype	Female carriers (~50%) may have a learning disability, intellectual disability, behavioral problems, or seizures.

ADDITONAL RISK GENES

WNT10A-related disorders (WNT10A)	Dosage Effect	Some individuals may have congenital absence of one or more teeth (isolated tooth agenesis) or mild symptoms of hypohidrotic ectodermal dysplasia.
Bloom Syndrome (BLM)	Novel Phenotype	Colorectal cancer

Discussion

- The original purpose for carrier screening was to identify asymptomatic carriers of autosomal and X-linked recessive monogenic disorders that primarily affected neonates and children/adolescents so as to allow for preimplantation or prenatal testing for at-risk couples and pregnancies.
- The time that has passed since the initial use of such screening has now allowed for the observation of individuals who were identified to be carriers of pathogenic variants in ostensibly recessive conditions and now present with adult-onset conditions that may be related to their heterozygote status.

Discussion

- Rigidity in the classification of genetic disease did not allow for what we now understand to be is that pathogenic variants can impact gene function and clinical outcomes in ways that were not initially associated with the presence of a pathogenic variant as they did not impact pediatric health and wellbeing.
- Our expanding ability to sequence the genome and determine the presence of variants not initially associated with disease development now allows for genetics and genomics to have a far greater impact on the diagnosis, prevention and treatment of disease as well as a greater understanding of the genetic and genomic role in clinical conditions not previously associated with genomic variants.
- But with greater impact comes greater responsibility for genetics providers – and much of that responsibility will lie with genetic counselors

Counseling

- Reporting the presence of pathogenic genes found on a carrier screen panel can no longer just be presented to patients as a finding that is of “no concern;” not from a somatic viewpoint or even a reproductive viewpoint
- Counselors, geneticists and clinicians who provide carrier screening MUST have knowledge and understanding of the increasing likelihood that a variant in a particular gene may have somatic and reproductive implications not previously recognized in a rigid system characterizing conditions as either recessive or dominant.

Counseling

- At Northwestern Medicine, all individuals undergoing carrier screening are informed prior to testing that results are primarily to assess for fetal risk for monogenic disorders but also may identify gene mutations that could impact the health of individuals found to be carriers of pathogenic variants for certain genes.
- At Northwestern Medicine, a total of 62 genes encompass the screening outcomes that lead to additional counseling when pathogenic variants are identified in individuals seeking carrier screening.

Conclusions

- Indeed, those of us who provide counseling of at-risk couples, along with interpreting PGT-M outcomes, will need to incorporate this expanding and changing understanding of the clinical manifestations of pathogenic variants in the development of disease, especially in disease conditions that may not present until adulthood.
- Yes, this means that some heterozygote embryos may now be considered “affected” and not suitable for transfer. Not affected with the classical autosomal recessive condition, but with an increased risk for morbidity and potentially early mortality that may appropriately bias clinicians and patients alike in their choice of embryo(s) to transfer.

Conclusions

- Just when we all thought that the use of expanded carrier screen would be a great step forward in reducing/eliminating genetic disease…
- We were right. But not for the reasons that we initially considered. In fact, it's our increasing ability to sequence the genome and identify variants that makes carrier screening, along with improved sequencing technology, a far better tool in improving outcomes for those who present for IVF and PGT, even if previously held clinical norms will need to be changed to reflect our changing understanding of the potential of pathogenic variants to cause disease at all ages.
- Further analysis of the genome will likely identify variants and sequences that may impact reproductive outcomes without being associated with postnatal disease development.
- As with most other genetic clinical issues, it will be mostly left to genetic counselors to inform and educate our patients (and colleagues) of this new concept and empower them to make choices that are right for them.

Thanks to

- **Katie Abihider CGC**
- **Melissa Damrongvachiraphan CGC**

for their invaluable help and assistance in making this presentation possible.

- Svetlana Rechitsky, Reproductive Genetics Innovations
- Jeremy Grushkow, Juniper Genomics
- Sherman Elias and Joe Leigh Simpson

THANK YOU