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PACIFIC WAVES - EXPLORING SCIENTIFIC FRONTIERS IN AN EVOLVING SOCIETY
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Medical Update and Adverse Outcome Management in Third Party Reproduction

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Disclosure

- Full time employee of Inception Fertility

Learning Objectives

1. Identify when new medical information from below warrants follow up
   - Gamete donor
   - A patient/recipient
   - Pregnancy or child conceived from donor gametes

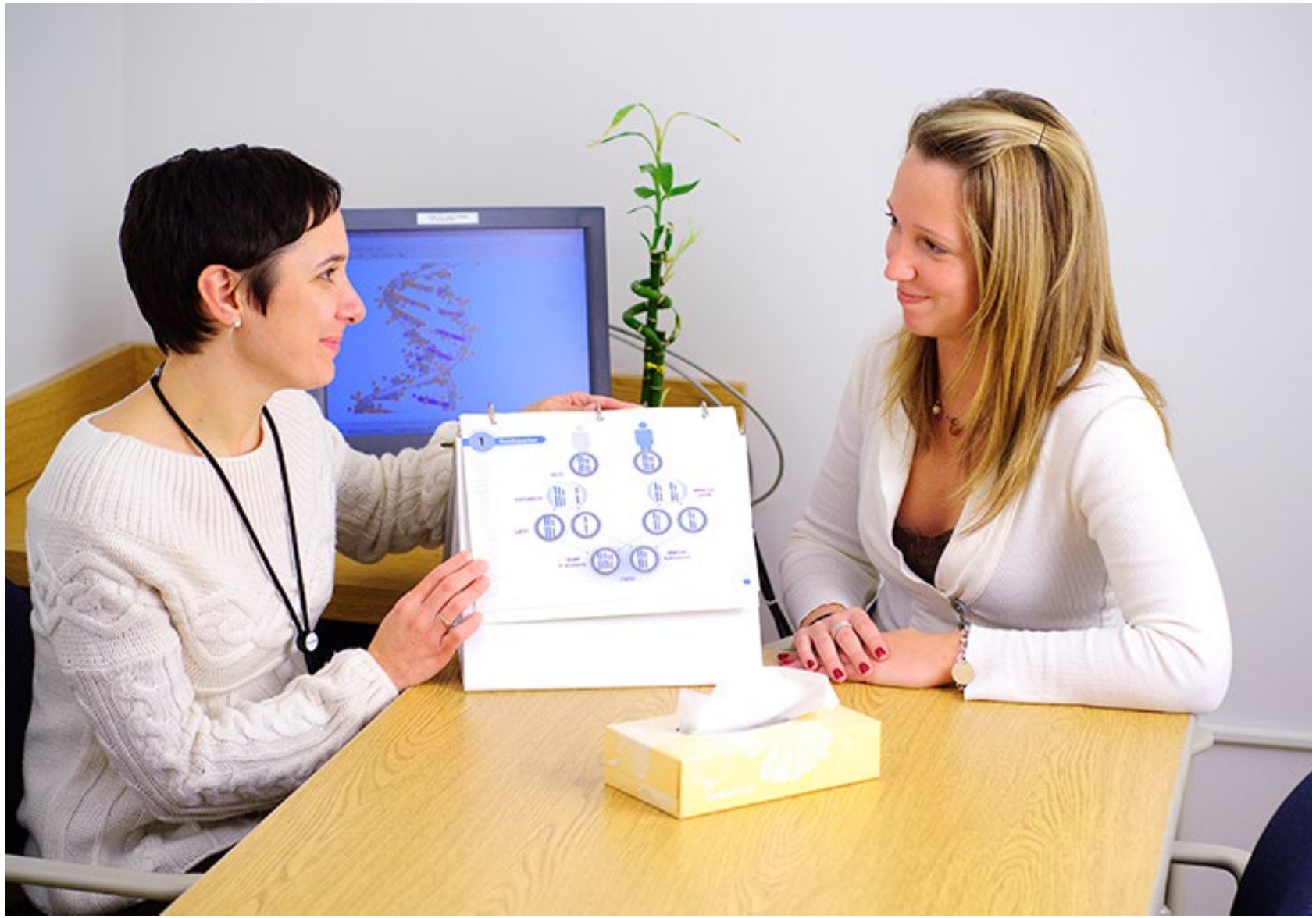
2. Review for Clinic and Donor Program
   - Information essential for accurate risk assessment
   - The importance of medical records
   - Notification of impacted recipients and donors

3. List of possible follow up testing
   - Genetic testing of gamete provider(s), child or donor conceived person (DCP)
   - Preimplantation genetic testing
   - Prenatal testing

What we are NOT tackling in today's talk

…logistics of sharing medical updates with donor conceived persons.

Genetic Risk Assessment



The objective of genetic risk assessment in fertility care is to identify reproductive genetic risk and offer risk reducing options.

Genetic risk assessment is a dynamic process that can change as new medical information arises during or after treatment.

Our First Tool: Personal and Family Medical History

For recipients, can be obtained by the following methods:

- Questionnaire
- Discussion with fertility care provider
- Consultation with a certified genetic counselor

For egg donors, can be obtained through:

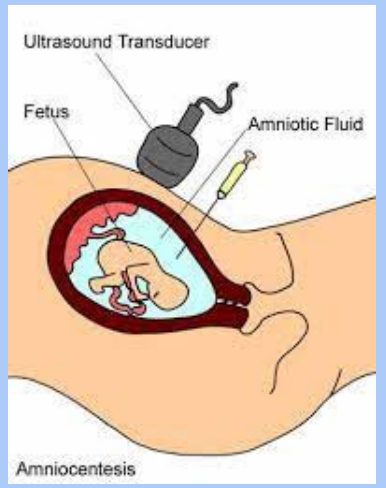
- Donor application
- Consultation with a certified genetic counselor

Additional Tools for Assessing Reproductive Risk

- **Genetic Carrier screening** – expanding numbers of genes on panels to screen for autosomal recessive or X-linked conditions

- **Preimplantation genetic testing (PGT)**
  - Aneuploidy – PGT-A
  - Structural Rearrangements – PGT-SR
  - Monogenic (single gene) conditions – PGT-M

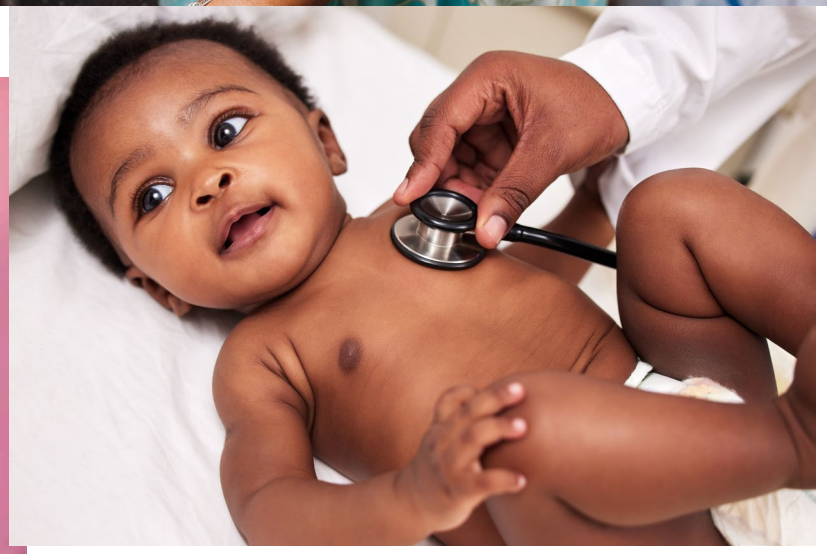
- **Prenatal testing**
  - Screening options
    - fetal imaging
    - maternal serum screening
    - cell free DNA (NIPS or NIPT)
  - Diagnostic options
    - chorionic villus sampling (CVS)
    - amniocentesis



Family history review, genetic carrier screening, PGT and prenatal testing ***cannot identify all*** causes of:

- developmental delays, learning problems, autism
- health problems
- birth defects
- genetic disease

Medical Updates in Third Party Reproduction



Medical Updates vs Adverse Outcomes

- A **medical update** is new information received after initial screening is complete and may include:
  - new genetic test results (carrier screening or diagnostic)
  - personal and family history updates for donors and donor conceived children
  - pregnancy outcomes for recipients and donors

- Often, we use the term **adverse outcome** when the new information may have a negative emotional impact or repercussions for recipient or donor's:
  - future reproductive decision making
  - current pregnancy
  - children

There is a movement toward calling all new information a medical update as opposed to an adverse outcome to lessen the stigma of the information.

What do we do when…

- A recipient reports her baby had a positive newborn screen for genetic disorder
- A previous egg donor reports her pregnancy is affected with a severe birth defect
- A recipient shares that she ended a pregnancy affected with anencephaly
- A previous egg donor shares new personal medical diagnosis

…any of this information could change the consideration for genetic testing or medical management.

Show of hands:

Does your clinic or egg bank have a documented standard operating procedure (SOP) for managing medical updates in third party reproduction?

Yes…No…Don’t Know?

Adverse Pregnancy Outcomes

- Pregnancies or children diagnosed with
  - major malformations* on fetal ultrasound and/or after birth
  - A genetic condition
  - A significant medical and/or developmental issue

- Some examples of adverse outcomes:
  - Cleft lip and/or palate
  - Spina bifida or anencephaly
  - Congenital heart defects
  - Chromosome copy number changes (whole or partial aneuploidy)
  - Autism or intellectual disability
  - Fetal Cystic Hygroma
  - Single Gene Conditions (e.g., cystic fibrosis, neurofibromatosis, etc)
  - Late pregnancy loss with fetal abnormalities

**CDC website defining major malformation:*
https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/chapters/chapter-1/chapter1-4.html

Challenges in Adverse Outcomes

- Continued communication with the reporting individual
  - May be long periods of time to get more details
  - Individual may discontinue communication

- Sensitivity in receiving the information, as well as in responding and requesting more information is essential as the reporting individual may be feeling
  - Overwhelmed
  - Emotional
  - Despair
  - Confusion
  - Anger
  - Guilt
  - Shame
  - Need to blame or hold others accountable

The who, what and why of a successful investigation

Who should be on the team:

- MDs
- Clinical staff (RNs, NPs, PAs, etc)
- Genetic counselors
- Third party staff

What is important in the investigation:

- Communication with reporting individual and their care providers (MFM, pediatricians, genetic counselors, etc.)
- Medical records documenting the diagnosis (fetal ultrasounds, DNA testing, chromosome testing, genetic consult reports, etc.)

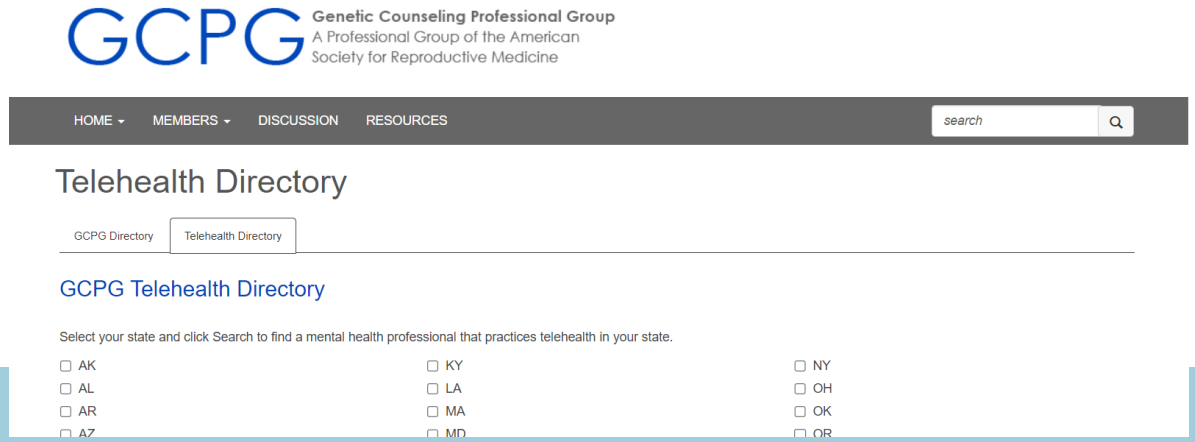
Why medical records are critical:

- Confirm accuracy of initial report
- Determine if there is additional information that wasn't relayed
- Get a full picture of the diagnosis or differential diagnoses

Genetic Counseling Resources

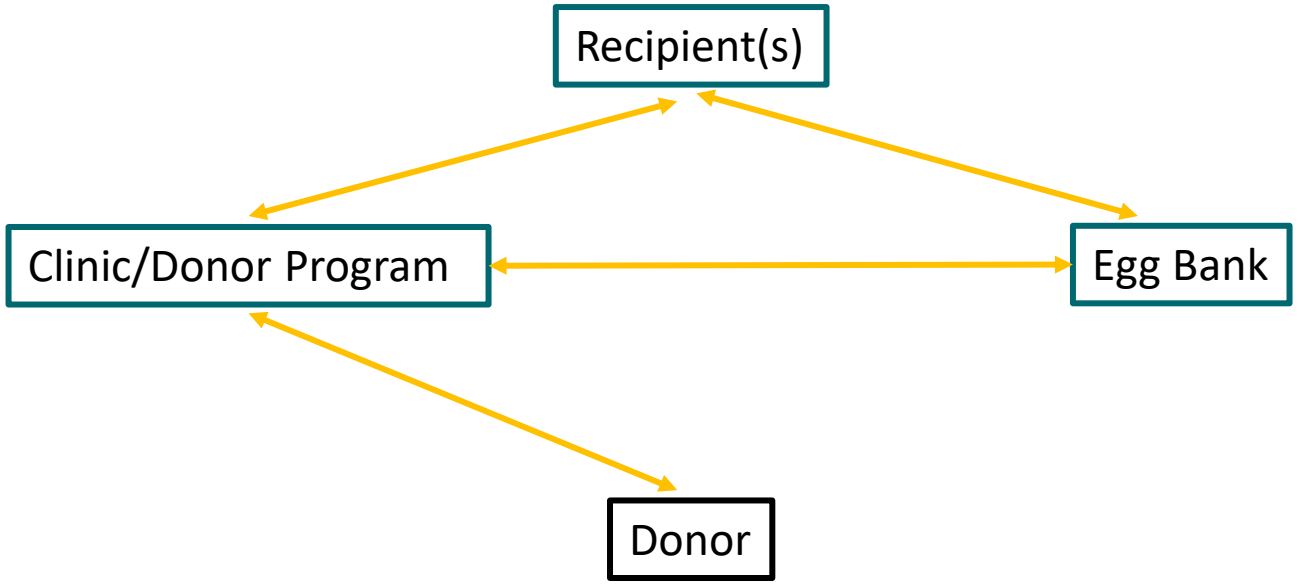
- Ways to incorporate genetic counselors into your practice
  - In-house genetic counselor
    - Full or part time employee
    - Independent contractor
  - Telemedicine genetic counseling vendors
  - Partner with local reproductive genetic clinic's genetic counselors (i.e. prenatal diagnosis center)

- ASRM Genetic Counseling Professional Group – look up tool
  (https://connect.asrm.org/gcpg/network/telehealth-directory)



Keys to a Successful Investigation

- Multidirectional sharing of information and collaboration



- Clinic where reporting recipient case is identified facilitates information obtainment (communication with recipient and medical records obtainment)

- Donor program/egg bank coordinates notifications of other impacted recipients and donor, and possible additional testing on donor

Notification with Third Party Reproduction

- When a gamete donor is involved in an adverse outcome, the information may impact many people:
  - The reporting recipient and their embryos, pregnancies and children
  - Other recipients and their embryos, pregnancies and children
  - The donor and their pregnancies and children
  - The donor's family
- Notification needs to include:
  - Description of the condition
  - Inheritance pattern
  - Recurrence risk
  - Info on available testing of embryos or pregnancy to reduce risk
  - Info regarding possible medical management to reduce risk
- **Notification can be time sensitive**

Notification Prioritization And Responsibility

- If increased risk from medical update is determined, notification of other recipients and donor should be prioritized as follows:
  1. Current pregnancies*
  2. Frozen embryos, with planned FET*
  3. Frozen gametes, with planned insemination*
  4. Frozen embryos, no current plan for FET
  5. Frozen gametes, with no current plan for insemination
  6. Children, but no remaining gametes/embryos (if indicated)

  **Preliminary partial notification may be warranted*

- The donor gamete bank is responsible for notifying recipients receiving care outside of the reporting recipient's clinic.

- NOTE: If no increased risk is determined from the medical update, proactive notification may not be required but information can be stored and available for recipient view

Which medical updates warrant proactive notification?

- Is it **actionable** information?
  - is there any testing available to address concern?
  - might it affect a recipient's decision to use remaining gametes or embryos?

- Does the medical update have an **increased chance of happening again (recurrence risk)** which is greater than the general population background risk?

- What is the quality of the report (i.e., **medical records documenting a diagnosis** vs patient mentioning that her child's pediatrician is monitoring for a possible concern)?

- Would this history have made the donor **ineligible** in the initial screening period per **ASRM*** guideline?
  - Major vs minor malformation per CDC (*https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/chapters/chapter-1/chapter1-4.html*)
  - Potentially dominant or X-linked condition

Is the Donor Still Eligible?

- If investigation identifies an **increased risk for major[1] medical or developmental conditions** in donor conceived pregnancies and/or children, the **donor is further considered ineligible[2]**
  - Donor's profile should be **unavailable for new recipients** to view or select
  - Any purchased unused gametes should be recalled/replaced
  - Case by case consideration of sibling cycles

- If the increased **risk is low or remains unclear** after investigation
  - **Unavailable for new matches, but sibling cycle may be considered**
  - Recipients should receive genetic counseling from a certified genetic counselor
  - Waiver could be signed acknowledging increased risk prior to next cycle

- If investigation determines there is **no increased risk** to donor conceived pregnancies or children, or if the adverse outcome is determined to be minor*
  - **Donor is still eligible**; may remain available for repeat and new selections
  - Genetic risk assessment report and donor profile may be addended to reflect update (case by case determination)

[1]per CDC reference (1.4 Congenital Anomalies - Definitions | CDC)

2 ASRM Guidance Regarding Gamete and Embryo Donation 2021

The Importance of Medical Records

- Recipient reported to the clinic/donor program that her child was born with a congenital heart defect (ventriculoseptal defect) which was repaired at 4 months of age with no other problems.

- A notification letter was sent to other recipients ***based on patient report only***, informing of:
  - 1-3% recurrence risk for half siblings of the affected child.
  - PGT-M is not possible for isolated heart defects based on presumed multifactorial inheritance
  - fetal echocardiogram is indicated for pregnancies conceived with this donor's eggs.

- ***Medical records were later received*** which indicated multiple congenital anomalies for the child, suggestive of a genetic syndrome.

- Whole exome sequencing had been ordered. Depending on the findings, recurrence risk can range from negligible to up to 50%.

- If additional testing for the donor is indicated and results are positive
  - PGT-M might be indicated for remaining sibling embryos
  - greater impact on other recipient's decision to use their remaining embryos

Evolution of Information

- Recipient reported that her child was diagnosed autism spectrum disorder (ASD) in 2019
- A notification letter was sent to other recipients based on patient report informing of the 1-3% recurrence risk for autism for half siblings of the affected child.
- Another recipient reported in late 2022 of an additional ASD diagnosis in her twins. The case was re-opened and multiple additional outcomes were discovered and reported, including
  - Pediatric cancer (likely multifactorial or sporadic)
  - Cleft palate (multifactorial)
  - Osteogenesis imperfecta (likely de novo)
  - Epilepsy (multifactorial)
  - Juvenile arthritis (multifactorial)
  - Third case of autism (possibly multifactorial, but genetic testing initiated)

- A second notification was sent to all recipients with the updates.
- Pending evaluation and genetic testing for one of the children with autism may lead to a third notification when results are available.

To date, no professional guidance…

…so, we'll create it!

- Collaboration of genetic counselors working in fertility clinics, donor gamete facilities, and advocacy to determine best practices for medical updates with gamete donors and donor conceived persons

- Manuscript submitted in April 2024 for hopeful publication in ASRM's *Fertility and Sterility:* "Management of Medical Updates on Gamete Donors and Donor-Conceived Persons" – decline; submitted to Genetics in Medicine 2025

- STAY TUNED…

Summary

- Three means of assessing genetic risk in a fertility setting:
  1. Personal and family history review for recipients and gamete donors
  2. Genetic carrier screening of recipients and gamete donors
  3. Preimplantation genetic testing

- Medical updates can impact care and reproductive decision making

- Adverse outcomes need investigation to determine if additional genetic testing or treatment is warranted to address risk in subsequent care

- Genetic counselors can assist with investigation, provider support, additional testing coordination and patient counseling

Q&A