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Investigating Uptake and Impact of Genetic and Genomic Evaluation Following a Perinatal Demise

THESIS

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by

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DEDICATION

To

Genevieve D'Orazio, who was always asking the right questions

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ABSTRACT OF THE THESIS

Investigating Uptake and Impact of Genetic and Genomic Evaluation Following a Perinatal Demise

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Despite public health efforts to mitigate stillbirth and neonatal death over the 20th and 21st centuries, the rate of decline in perinatal death has plateaued. Genetic etiologies, especially those implicated in undiagnosed causes of perinatal death, are thought to contribute to this trend. Ample literature has investigated the diagnostic yield of genetic testing in the case of stillbirth and neonatal demise. However, little research has explored the frequency of involvement of trained genetics specialists, such as medical geneticists and genetic counselors, in perinatal death cases from prenatal ascertainment of anomalies to demise. The current study examined retrospective demographic and clinical data from 111 perinatal demise cases and their gestational parents associated with attendance and uptake of prenatal genetic counseling, post-delivery genetics consult, genetic/genomic testing, and autopsy investigation at a large university-affiliated medical center between November 1st, 2017, and December 1st, 2021. Furthermore, this study investigated the potential diagnostic yield of genetic testing in the presence and absence of genetics specialist involvement providing evaluation and testing recommendations. Finally, this

study appraised the degree of patient education in genetic post-counseling documented by genetics specialists versus non-genetics specialists. Through univariate analysis, genetic specialist involvement in perinatal cases was found to be associated with significant increases in genetic testing uptake ($p=0.007$), abnormal genetic testing results ($p<0.001$), positive results and results of uncertain significance that have a potential to contribute to disease), and increased degree of documentation of patient education outcomes through genetic post-test counseling compared to those services rendered by non-genetics providers ($p<0.001$). The findings of this study underscore the importance of active integration of genetics healthcare professionals into the process of perinatal postmortem investigation and allocating the practice of genetics evaluation and genetic testing selection to healthcare professionals with relevant genetics training.

I. INTRODUCTION

1.1 Defining perinatal mortality

Perinatal mortality is defined as the summation of fetal deaths (stillbirths) and neonatal deaths. According to the U.S. National Center for Health Statistics, fetal death is defined as "the delivery of a fetus showing no signs of life as indicated by the absence of breathing, heartbeats, pulsation of the umbilical cord, or definite movements of voluntary muscles" (MacDorman & Gregory, 2015). Though the fetal period of prenatal development begins at the 8th week of gestation, suggested reporting requirements for fetal death start at the 20th week of gestation or greater or at a birth weight greater than or equal to 350 grams (National Center for Health Statistics, 1992). Similarly, stillbirth is defined as a fetal death or pregnancy loss that occurs after 20 weeks of pregnancy and before or during delivery, not including fetal losses due to elective termination of pregnancy (Hoyert & Gregory, 2016). Infant deaths are categorized as deaths of liveborn infants within the first year of life. Neonatal deaths (under 28 days) are further defined as early neonatal (under seven days) or late neonatal (7-27 days) deaths. The World Health Organization considers neonatal death to include the 28th day of life (Guevvera, 2006).

Perinatal mortality as a category is not defined as a vital event, which includes the reporting of live births, deaths, and fetal deaths; instead, it is a distinction used primarily for statistical purposes. Furthermore, the fetal mortality rate of at least 20 weeks and infant mortality rate are comparable (5.70 fetal deaths at 20 or more weeks of gestation per 1,000 live births and fetal deaths in and 5.6 infant deaths per 1,000 live births in 2019) (Kochanek *et al.*, 2020; Gregory *et al.*, 2021). Several definitions of perinatal mortality exist,

as defined by the American Academy of Pediatrics' Standard Terminology for Fetal, Infant, and Perinatal Deaths. This study will implement Definition II of perinatal demise, which defines the category as fetal deaths with a stated or presumed gestational age of 20 weeks or more and infant deaths that occur on or before 28 days of life (Barfield *et al.*, 2016).

1.2 Addressing the burden of perinatal mortality

Overall assessment of perinatal demise statistics in the United States shows that the nation has experienced a steady decrease in stillbirth and neonatal deaths through the 20th and 21st centuries. According to the American College of Obstetricians and Gynecologists (ACOG), "information from vital records is critical to identify and quantify health-related issues and measure progress toward quality improvement and public health goals." ACOG asserts that such documentation is crucial for serving as a proxy for the nation's health, "thereby influencing policy development, funding of programs and research, and measures of health care quality" (ACOG Committee Opinion No. 748, 2018). From 1982 to 2017, stillbirths have decreased by 32.9%, from 8.5 stillbirths per 1000 births to 5.7 stillbirths per 1000 births in the US (Dongarwar *et al.*, 2020). Neonatal deaths have experienced a more dramatic decline, from 7.7 to 3.8 deaths per 1000 live births, a 51% decrease (Levels and Trends in Child Mortality, 2021).

Advancements in medical screening and public health protocols and programs can account for the decrease in perinatal deaths with and without genetic etiologies. Access to pre-pregnancy and early prenatal care has reduced infant mortality. In a study of infant mortality rate risk factors in pregnancies between 1989 and 1995 in Chicago, IL, odds ratios for infant mortality increased four-fold with no prenatal care throughout the

pregnancy and two-fold with inadequate prenatal care, defined as prenatal care that began in the third trimester of pregnancy (Poma, 1999). In bridging disparity gaps in medically underserved populations, programs such as the Maternal Infant Health Program (MIHP), providing Medicaid-enhanced prenatal care programs in the state of Michigan, have been shown to reduce the odds of death in the first year of life, with early enrollment into MIHP reducing odds of infant death further (Meghea *et al.*, 2015).

Public health programs extending into the newborn period have stemmed the rate of demise from rare diseases, with newborn screening allowing-for the identification of multiple genetic conditions using blood samples from newborn infants. From its inception, the number of conditions screened for by newborn screening programs across the US has increased from one with the screening of phenylketonuria in the 1960s to 35 federally recommended conditions through the Recommended Uniform Screening Panel (2018). When combined with Medicaid adoption, newborn screening was found to have prevented an estimated 9.4 fewer deaths per 100,000 births between 1959 and 1995 (Sohn *et al.,* 2019). Furthermore, the Safe to Sleep Campaign, first implemented in 1994, educated caregivers regarding the importance of back sleeping in newborn infants in preventing instances of sudden infant death syndrome (SIDS), sudden unexpected infant death (SUID), and other sleep-related causes of infant death (Tanabe & Hauck, 2018). Between the inception of the Safe to Sleep Campaign and 1999, the overall SIDS rate dropped by more than 50% (Moon & TASK FORCE ON SUDDEN INFANT DEATH SYNDROME, 2016).

Despite advancements in medical screening and public health programs targeting prenatal and newborn outcomes, perinatal death declines have stagnated through the 21st century. From 2007 to 2017, neonatal deaths have experienced a downward trend from

4.42 to 3.85 per 1000 live births, a decrease of 13%. In recent years, this downward trend has plateaued or even reversed as is the case with preterm stillbirths increasing by approximately 6.5% (4.11% to 4.38%) from 2007 to 2017 (Dongarwar *et al.*, 2020). It is concerning that this downward trend of the US's perinatal death rate has plateaued, and declines have begun to lag behind those of other industrialized nations. Countries with a similar gross domestic product (GDP) to the US, including France and the UK, had 3.8 and 3.9 infant deaths per 1,000 live births, respectively, in 2018, compared to the US's 5.7 infant deaths in 1000 live births (OECD, 2021). This difference is despite the US spending almost twice as much as countries with similar GDP and healthcare utilization rates as the US (Papnicolas *et al.*, 2018). Driving forces of the plateauing of infant mortality rate in the US are not well-understood, though wider ranges of education level, occupation, income, and ethnic disparities among US mothers compared to other industrialized countries have been suggested to play a substantial role (Chen *et al.*, 2016). Additionally, inadequate prenatal care, when compared to adequate prenatal care as defined by the American Congress of Gynecologists and Obstetricians as prenatal care beginning in the first trimester with regular prenatal visits until delivery, has been associated with increased risk of prematurity, stillbirth, early neonatal death, late neonatal death and infant death (Partridge *et al.*, 2012). Pregnancy outcome disparities are often attributed to poor access to prenatal care. Racial disparities in the incidence of stillbirth persist, even amongst pregnant individuals with equal access to prenatal care (Stillbirth Collaborative Research Network Writing Group, 2011).

1.3 Overview of causes of fetal and infant death

In approaching the problem of the perinatal death rate, more research is needed to define the utilization of prenatal and postnatal services in pregnancy preceding a perinatal demise, especially in those deaths without a diagnosis. Indeed, despite efforts nationally and globally to study fetal and infant mortality and address common causes of perinatal death with public health efforts and relief, the etiology of fetal and infant deaths commonly goes unexplained. In a study to elucidate the causes of death for 512 fetuses, 312 stillbirths were determined to have a probable cause, while an additional 78 stillbirths were found to have a possible cause (Stillbirth Collaborative Research Network Writing Group, 2011). Even when anomalies in pregnancy are identified, cases of perinatal death can go without a confirmed cause of death. Tables 1 and 2 list common causes of death in the case of stillbirth and neonatal death, respectively.

Table 1. Causes of stillbirth (Adapted from the Stillbirth Collaborative Research Network Writing Group, 2011)

Cause of Death	Examples	Percent of Stillbirths
Pregnancy and labor complications	Preterm labor, pregnancies with multiples, or placental abruption	29.3 (Most common cause of stillbirth <24 weeks)
Placental complications	Uteroplacental insufficiency	23.6 (Most common cause of stillbirth >24 weeks)
Birth defects	Structural defects with and without a known genetic etiology	13.7
Umbilical cord abnormalities	Prolapse, strictures, and thrombosis	10.4
Hypertensive disorders	Chronic hypertension, preeclampsia	9.2
Maternal medical complications	Diabetes, antiphospholipid syndrome	7.8

Table 2. Causes of neonatal death (Adapted from the Infant Mortality by Age at Death in the US from the National Vital Statistics System (NVSS), 2016)

Cause of Death	Examples	Deaths per 100,000 live births
Low birthweight	Intrauterine growth restriction	97.7
Congenital malformations	Neural tube defects, congenital heart defects, omphalocele, microcephaly	86.4
Maternal complications	Infection, hypertensive disorders	35.3
Placenta, cord, and membrane complications	Nuchal cord, vasa previa, single umbilical artery	21.0
Bacterial Sepsis	Caused urinary tract infections, lung infections, or abdominal incision infections	14.0

Even when a cause of death is determined, underlying etiology may be a challenge to ascertain. However, more research, especially in the case of complex genetic etiologies, is needed to unravel the causes of death in the perinatal period. Genetic disorders and conditions of a suspected genetic etiology are marked as leading causes of death in fetal and neonatal demise. Genetic conditions have been found to play a role in causes of death in the perinatal period, such as major congenital anomalies, including non-immune fetal hydrops, prematurity, and diagnoses of exclusion or in the case of a previously unknown cause of death, including SIDS and sudden and unexplained neonatal death (SUEND) (Sparks *et al.* 2020; Quinlan-Jones *et al.*, 2019; Wojcik *et al.*, 2018). As Wapner (2010) defines, genetic disorders in perinatal deaths can be categorized as cytogenetic (chromosome) abnormalities or monogenic ("single gene") disorders. Additionally, a genetic etiology is more highly suspected in stillbirth or neonatal death with multiple congenital anomalies without known teratogenic exposures. Uncovering a genetic diagnosis as the cause of a perinatal demise can provide information for establishing recurrence risks for future pregnancies and, if applicable, options for preconception and prenatal genetic testing, insight into medical interventions and treatment options prenatally and postnatally in the case of recurrence, and to provide emotional closure to the family.

1.3.1 Chromosomal abnormalities in perinatal demise and methods of cytogenetic analysis

The burden of cytogenic abnormalities in perinatal deaths is notable. One study found that 11.6% (67/573) of deceased infants had a major chromosomal abnormality, which comprised just over half of all genetic diagnoses confirmed (Wojcik *et al.,* 2019).

Cytogenetic abnormalities include whole chromosomal aneuploidy, or a different number of chromosomes than the expected 46 chromosomes in each cell, unbalanced chromosome translocations, microdeletions or microduplications of regions of chromosomes, or marker chromosomes in which there is an addition of a small fragment of chromosomal material that cannot be attributed to a specific chromosome through conventional chromosomal analysis. Approximately 10-20% of stillbirths possess an identifiable cytogenetic abnormality (Liu *et al.*, 2014). The most common cytogenetic abnormalities in stillbirths are similar to those found in liveborn infants, with full aneuploidies including monosomy X, trisomy 21, trisomy 18, and trisomy 13. The remainder of chromosomal anomalies involved in stillbirth includes mosaicism (the emergence of two or more genetically distinct cell lines following fertilization), unbalanced chromosomal rearrangements, and marker chromosomes. Most chromosomal abnormalities detected in fetal and newborn demises are thought to be the product of *de novo* changes, isolated to the conception, that occur during the formation of gametes or during embryonic development (Robio *et al.*, 2005). The remainder may be the result of inherited factors, such as the inheritance of an unbalanced chromosome rearrangement from a parent with a balance chromosomal rearrangement that can be elucidated with a parental karyotype.

With the advent of genetic testing, analyses such as the karyotype and the chromosomal microarray analysis (CMA) have been crucial for genetic investigations of perinatal demise. A karyotype visualizes the gross structure of chromosomes during cell division during the metaphase stage when the chromatin (loose threadlike structure of the chromosomes) is at its densest. Karyotype analysis is best used to detect numerical chromosomal abnormalities and large balanced and unbalanced chromosomal structural

rearrangements. However, karyotype requires living tissue that is viable to divide in culture, limiting options for sample type and preservation. In the case of spontaneous abortion (SAB) and intrauterine fetal demise (IUFD) samples, cell culture failures in preparation for chromosomal analysis occur 25% to 50% of the time (Baxter & Adayapalam *et al.,* 2013; van den Berg *et al.,* 2012; Zhou *et al.,* 2016). In embarking on genetic evaluation following a SAB or IUFD, specimen collection must be well-timed to ensure a viable sample for genetic analysis. CMA analysis, conversely, can also be performed on archived tissues, such as those preserved in formalin-fixed, paraffin-embedded (FFPE) tissues. It can detect deletions or duplications of genetic information at a higher resolution than karyotype but cannot detect balanced structural rearrangements. Given the viable sample preservation available for CMA testing, it is unsurprising that CMA has a higher success rate than conventional chromosomal analysis in the case of post-mortem genetic analysis. In a metanalysis of seven studies spanning 2009 to 2018, the test success rate in conventional chromosomal analysis was 75% compared to 90% in CMA (Martinez-Portilla *et al.*, 2019). In a study analyzing the sample tissues of 532 stillbirths that had received karyotype across 59 hospitals, a reflex to CMA in these cases led to an approximate 42% relative increase in the rate of diagnosis of genetic abnormalities, with an approximately 54% increase rate in stillbirths with structural anomalies, than by karyotype alone (Reddy *et al.*, 2013).

Preliminary research has been done regarding the diagnostic yield of neonatal deaths that undergo cytogenetic analysis. In living neonates younger than 30 days of life treated in a cardiac intensive care unit for structural heart disease, approximately 18% of patients studied had a known chromosomal abnormality detected by karyotype and/or

fluorescent in situ hybridization (FISH), the usage of specially designed DNA probes that hybridize to and signal a known genetic sequence (Dykes *et al.*, 2016). In a cohort of neonates with hypotonia, karyotype analysis contributed to a clinical diagnosis in 41% of cases (Laugel *et al.*, 2008). Such results led to the study authors recommending cytogenetic analysis among first-tier evaluations for hypotonic neonates with facial dysmorphism.

The American College of Medical Genetics (ACMG) (Miller *et al.*, 2010) has recommended using CMA as a first-tier test in the postnatal evaluation of individuals with multiple congenital anomalies or neurodevelopmental delays. However, the current recommendation as a first-tier test does not extend to additional applications of CMA in the prenatal or postmortem setting or in the case of SAB or IUFD. Citing the sufficient yield of genetic evaluation in cases of stillbirth, ACOG (2020) recommends the undertaking of genetic evaluation in all cases of stillbirth after obtaining appropriate parental consent.

1.3.2 Monogenic disorders in perinatal demise and methods of molecular analysis

However, a negative karyotype, CMA, or FISH assay cannot rule out the existence of a genetic change that exists below the resolution of cytogenetic analysis, such as a sequence change in a single gene. Single gene, or monogenic, disorders have been estimated to affect 14-16% of neonates and infants treated in intensive care units (Scholz *et al.*, 2021). Monogenic disorders result from genetic changes in nuclear genes. They can be categorized by inheritance pattern (how the condition is passed from generation to generation) as autosomal recessive, autosomal dominant, and X-linked inheritance. Autosomal recessive disorders are caused by biallelic variants, or a variant in both copies, of a given gene. Examples of autosomal recessive conditions implicated in stillbirth and neonatal death

include hemoglobinopathies (inherited blood disorders), autosomal recessive polycystic kidney disease, Smith-Lemli-Opitz Syndrome, peroxisomal disorders, and amino acid disorders (Wapner, 2010). In the case of autosomal recessive conditions, heterozygote individuals with a variant in only one copy of a disease-causing gene are said to be carriers of this condition and typically do not manifest the disease. Couples who are both carriers of the same variant for an autosomal recessive condition have a 25% chance of having a pregnancy affected by the condition.

In contrast, autosomal dominant conditions result from variants in a single copy of a gene and commonly have gain of function mechanisms that enhance gene products to deleterious ends. Examples of autosomal dominant conditions implicated in perinatal death include skeletal dysplasias, such as thanatophoric dysplasia, and Noonan spectrum disorders. Although autosomal dominant conditions resulting in perinatal death are commonly thought to be caused by *de novo* variants, isolated to the affected pregnancy, notable exceptions such as the inheritance of a channelopathy condition, such as Long QT syndrome, or the possibility of germline mosaicism (disease-causing variants limited to the sex cells of a parent) can lead to clinically actionable discussions of recurrence risk in future pregnancies or cascade testing of asymptomatic child or adult family members (Wapner, 2010; Wilders, 2012; Ackerman *et al.*, 2011; Ackerman, 2009).

Distinct from variants affecting the autosomes, X-linked conditions are genetic conditions caused by variants on the X chromosome. Such disorders, such as incontinentia pigmenti, oral-facial-digital type I, and microphthalmia with linear skin-defects syndromes, lead to lethal presentations in male fetuses. With only one X chromosome, males will experience a complete absence of protein products of X-linked genes inactivated by

pathogenic variants. This translates to a lethal phenotype in conditions affecting essential genes. X-linked conditions can be inherited by unaffected or mildly affected heterozygote mothers or occur *de novo* in the affected pregnancy (Wapner, 2010; Franco & Ballabio, 2006).

When a gestalt of anomalous features indicative of a specific condition is appreciated through physical exam, autopsy, or additional clinical evaluation, single-gene or multigene panels curated by clinical indication can be a targeted, cost-saving measure leading to diagnosis. High-throughput sequencing or next-generation sequencing (NGS) utilized in modern gene panels allows for the detection of base pair sequence changes as well as deleted or duplicated bases, depending on the assay. However, limited clinical history and the variable expressivity of genetic conditions can pose challenges to test selection and diagnostic yield of gene panels. Massively-parallel sequencing techniques such as exome and genome sequencing (ES and GS, respectively) have had significant gains in diagnostic yield over conventional methods of genetic analysis. Exome sequencing reads the genetic sequence of most of the patient's exome, the genetic information that codes for proteins. Genome sequencing reads the genetic sequences of the exome in addition to non-coding regions, such as introns, that hold information for regulatory elements crucial in the processes of transcribing the exome into proteins. Furthermore, regarding the use of ES and GS in the neonatal population, the ACMG (2021) recommends "*ES and GS as a first-tier or second-tier test (guided by clinical judgment and often clinician-patient/family shared decision making after CMA or focused testing) for patients with one or more [congenital anomalies] prior to one year of age […]*," specifically in the setting of trio testing (samples collected from the patient and both of their biological parents). Trio testing contextualizes

variants of uncertain significance against the backdrop of a close relative's genetic makeup. Furthermore, the ACMG's review found that when compared to conventional genetic testing methods, such as CMA, karyotype, single-gene testing or multigene panel testing, GS specifically had a 17% increase in diagnostic yield from 21% through standard methods to 38% in GS. ES and GS have confirmed and predicted increases in yield over multigene panel testing. In a cohort of 127 fetuses with nonimmune fetal hydrops, cases with a confirmed molecular diagnosis by ES were predicted to receive the same diagnosis by targeted gene panels 11-62% of the time, depending on the number of genes available on the panel (Norton *et al.*, 2022). Similarly, in a pediatric cohort with undiagnosed conditions with suspected genetic etiologies, a genetic diagnosis was made by GS in 41% of patients versus 24% by conventional targeted gene panel testing (Lionel *et al.*, 2018).

Though the overall contribution of chromosomal and monogenic conditions in the case of perinatal demise is thought to be significant, forming accurate estimations of the true impact of genetic disease in this cohort is challenging. Hays and Wapner (2021) argue that the genetic contribution in the case of undiagnosed perinatal illnesses is overestimated in studies where stillbirths and fetuses with multiple congenital anomalies have a high pretest probability of genetic diagnosis. However, this is not a function of poor study design as much as it is a common strategy to preserve resources in the case of patient care that utilizes costly, though potentially high-yield, tests such as ES and GS. In addition, genetic etiologies in perinatal populations may be underreported due to imprecise coding of causes of death recorded on death certificates. In a study by Wojcik *et al.* (2021), causes and contributors to death in a cohort of 115 infants recorded through the National Death Index (NDI) were analyzed for correlation with a laboratory-confirmed genetic disorder. Only

53% had an ICD-10 code in the category of "Congenital malformations, deformations, and chromosomal abnormalities" (Q00-Q99). Of those that did have an ICD-10 code reported as a cause of death in this category, reasons for chosen documentation of death included that the genetic cause of death was not known or suspected before submission to the NDI, the genetic diagnosis was listed as a contributor but not as a primary cause of death, or that the genetic diagnosis was listed as a cause of death through ICD-10 codes in a different range. These studies support the need for more widespread standardization of the process of studying and documenting genetic conditions in the event of perinatal demise.

1.4 Post-mortem evaluation and the role of genetics healthcare professionals

Previous sections have underscored the importance of a thorough examination of a fetus or neonate in the case of perinatal demise to determine the cause of death and, if indicated, proceed with appropriate testing on products of conception. This section will detail an overview of the basic perinatal post-mortem evaluation and how internal and external examination of perinatal remains, including dysmorphology exam, can aid in including or excluding the diagnosis of a genetic condition. Motivations for conducting perinatal autopsy vary widely between cases. The Royal College of Pathologists, a professional membership group for clinical pathologists in the United Kingdom, asserts in its perinatal autopsy guidelines that post-mortem evaluations following a spontaneous abortion in the second trimester serve to determine the reason for pregnancy loss while autopsies undertaken to investigate an elective pregnancy terminated in the case of fetal anomalies seek a diagnosis (Osborn *et al.*, 2017). Perinatal pathologist Linda Erst, MD, MHS (2015) suggests that when major congenital anomalies are appreciated prenatally by

ultrasound examination or postnatally through gross examination, a perinatal autopsy may be undertaken specifically to characterize or confirm the presence of congenital anomalies, assign a syndrome, sequence, or developmental field defect, or inform further diagnostic genetic testing. In each case, autopsy results can be a powerful tool in bringing closure to the family and informing future pregnancies based on informative results (de Sévaux *et al.*, 2019; Faye-Petersen, 1999).

The Autopsy Committee of the College of American Pathologists (1997) outlines practice guidelines for fetal or neonatal post-mortem evaluation. A perinatal pathologist ideally undertakes external and internal examinations of the fetal or neonatal specimen. The examination involves taking weights and measurements of bodily features and organs against standardized tables to ascertain gross pathology. Evidence of macroscopic and microscopic tissue pathology is also noted. Evaluation of maternal health, examination of the placenta, fallopian tubes, and uterus, when available, and appraisal of the history of the intrauterine environment are aspects of the fetal or neonatal autopsy distinct from the adult autopsy. This examination aims to identify an immediate cause of death and factors contributing to demise.

Perinatal autopsy remains the gold standard for solving perinatal death cases. Indeed, a large meta-analysis found that in 22-76% of cases that underwent perinatal autopsy, the invasive evaluation revealed new information of clinical importance not appreciated on prenatal ultrasound to aid in genetic counseling, including "establish[ing] the diagnosis of a syndrome, chang[ing] the prenatal diagnosis or determine[ing] the etiopathological mechanism of the anomaly" (Şorop-Florea *et al.* 2017; Godrijn *et al.*, 2002). Variability in ultrasound equipment quality, the skill of the ultrasonographer, early

gestational age at the prenatal ultrasound, and intrauterine environment (including the presence of polyhydramnios or oligohydramnios) can account for the significant variation in the number of anomalies missed by prenatal ultrasound but observed on perinatal autopsy (Şorop-Florea *et al.* 2017). However, despite the marked benefits of the perinatal autopsy, rates of uptake are in decline globally. Aspects such as national mandates for an autopsy for an unexplained death, quality of patient education during the consenting process, and patient cultural contexts such as religion, ethnicity, and experiences with media and public perceptions of autopsy all influence autopsy rate (Burton & Underwood, 2007).

Though no replacement for the invasive postmortem investigation, thorough genetic evaluation can provide invaluable information in the context of a suspected genetic etiology through largely non-invasive means. A medical geneticist and genetic counselor may undertake genetic evaluation in a perinatal death in the larger context of a perinatal healthcare setting. Medical geneticists and genetic counselors have complimentary skillsets but occupy distinct niches in a genetics healthcare team. Clinical geneticists in the United States are physicians that care for patients in a genetics clinic setting. These medical doctors are board-certified by the American Board of Medical Genetics and Genomics following extensive training in the evaluation, diagnosis, maintenance, and treatment of patients with genetic conditions across the lifespan (ACMG Careers in Medical Genetics, 2021). Even in the era of genomic medicine, extensive training in dysmorphology (i.e., the identification of subtle distinct physical features) that, in combination with disease symptoms, may indicate a specific genetic syndrome. A dysmorphology exam may aid in informing targeted panel testing for indicated conditions or corroborate genetic testing

results from broad testing methods such as genomic microarray, ES, or GS by correlating genotype with phenotype. Clinical geneticists may also receive training in additional medical specialties, such as obstetrics, maternal-fetal medicine, or pediatrics, positioning them as referral destinations during or following a pregnancy with confirmed structural anomalies for further evaluation.

Genetic counselors are non-physician healthcare professionals who receive extensive training through an accredited 2-year master's program in the clinical evaluation of a patient's medical history and family history to generate recommendations for genetic testing. More specifically, in the prenatal setting, genetic counselors evaluate indications that are at high risk for genetic conditions, including advanced maternal age of the mother, maternal serum screening results, obstetric history of multiple miscarriages, family history of a genetic condition, or observance of fetal ultrasound anomalies in the context of the parents' personal medical and family history to provide education regarding etiology, natural history, medical management options, testing options, and support resources in pregnancy (NSGC, 2008). Beyond delivering patient education and assessing genetic testing options, genetic counselors are also trained to provide psychosocial counseling and culturally appropriate support to address the patient's unique emotional context at each step of the genetic counseling process.

Regarding physicians responsible for ordering genetic testing, ACOG recommends that obstetrician-gynecologists (OB-GYNs) be well-versed in the benefits, limitations, and pre- and post-test counseling discussion points that concern testing ordered. However, the practice bulletin concedes that although testing is recommended in specific patient encounters (e.g., fetal aneuploidy may be offered to women early in pregnancy), the specific

type of test is not stipulated. Furthermore, the practice bulletin concludes that if the OB-GYN is not comfortable with ordering and discussing the implications of indicated genetic testing, the patient should be referred to a genetics specialist, such as a genetic counselor, maternal-fetal medicine specialist, or medical geneticist, for the condition to be appraised further for testing (ACOG, 2017). Given this recommendation, there are documented benefits of genetics healthcare providers supporting non-genetics providers in ordering genetic testing. In a large-scale study investigating the rate of prior authorization of genetic testing across ordering medical specialties, OB-GYN, genetics, and endocrinology were found to have the highest rates of prior authorization approvals compared to other ordering specialties, including family medicine, neurology, and internal medicine (Bajguz *et al.* 2021). These findings provide evidence that genetic healthcare providers are among the most successful at securing recommended genetic testing for patients. However, this study found that genetics healthcare professionals as ordering providers only contributed to 8.4% of the total genetic testing in the study. Since genetic counselors are not permitted to order genetic testing in most states, these data may underestimate the impact genetic counselors have on successful and equitable testing attainment, especially in a prenatal or perinatal setting. Furthermore, a qualitative study investigating the attitudes of neurologists and endocrinologists who routinely order genetic tests for patients called for a multidisciplinary approach to seeing patients with suspected genetic conditions in concert with genetics providers. Participants have cited a lack of access to onsite genetics professionals as a barrier to these ideal collaborative arrangements (Pasquier *et al.*, 2022).

Genetic counselors are at the forefront of attempting to bridge the gap in supporting and demystifying the postmortem genetic testing process. The National Society of Genetic

Counselors Cardiology Special Interest Group houses the Post-Mortem Working Group, which provides resources for patients and ordering providers to explore information about ordering genetic testing in the event of a miscarriage or sudden unexplained death and connect families to genetic counselors who specialize in post-mortem indications to discuss further steps for genetic testing, implications for recurrence risk of the condition in the family or future pregnancies, and providing closure to those affected by the death (NSGC, 2018).

1.5 Impact of the COVID-19 pandemic on uptake of prenatal care in the US

The onset of the COVID-19 pandemic resulted in significant burdens and alterations to care for the US pregnant population. As described, uptake of prenatal services in the first trimester with regular attendance to scheduled prenatal appointments is integral to maintaining adequate care during pregnancy. However, the tumult of the COVID-19 pandemic required the postponement of many non-essential or elective healthcare services to prevent viral transmission in clinics and allocate healthcare resources to mitigating loss of life due to COVID-19. These healthcare infrastructure changes led to significant reductions in antenatal and postnatal care attendance. One US study found that 53.4% of surveyed pregnant individuals reported having prenatal appointments canceled or rescheduled due to pandemic protocols, either at the behest of the health care provider or by the patient. These changes in patient care may have led to fewer face-to-face encounters, except for essential physical exams, screening, and imaging. More research is needed to determine if reductions in face-to-face prenatal visits impacted pregnancy outcomes following the onset of the COVID-19 pandemic.

There is preliminary evidence to suggest that there has been an increase in stillbirths during the COVID-19 pandemic compared with the pre-pandemic period. One study found an increase of approximately seven stillbirths per 1000 live births in a UK hospital cohort. The findings were notable because none of the recorded stillbirths during the pandemic period were associated with COVID-19 infection (Khalil *et al.*, 2020). However, these findings vary by study area. A study that measured preterm and stillbirth rates pre-pandemic and during the COVID-19 pandemic in Ontario, Canada, found no significant difference in rates between the two study periods (Shah *et al.*, 2021). Yet another study found that stillbirth rates increased while late preterm infant births decreased from pre-to post-pandemic onset (Curtis *et al.*, 2021). More investigation is needed to explore the association between changes in prenatal care structure and attendance and stillbirth and neonatal death rates.

1.6 Purpose and aims of the study

Through retrospective chart review of perinatal demise cases (utilizing Definition II of perinatal demise as described in this introduction) seen at the University of California, Irvine Medical Center (UCIMC) in Orange, CA, and through UCI Genetics Division Neonatal Intensive Care Unit (NICU) consult, this study aims to elucidate the impact of the involvement of genetics professionals versus non-genetics professionals in a tertiary care center serving a diverse patient population. As the selected study period includes the beginning of the COVID-19 pandemic (March 11, 2020, to December 1, 2021), it also provides a unique opportunity to gather evidence of the impact of pandemic-era stressors on patient care. To achieve this aim, the study will:

I) Determine the genetic diagnostic yield of perinatal demise cases, comparing the yield of those that do receive a dysmorphology exam by a medical geneticist with those that do not. It is hypothesized that perinatal demise cases that receive a dysmorphology exam by a medical geneticist will have a greater proportion of genetic diagnoses confirmed than those that do not receive a dysmorphology exam by a medical geneticist.

II) Investigate which gestational parent and perinatal decedent factors are associated with uptake of genetic testing post-delivery genetics consult. It is hypothesized that gestational parent factors related to the uptake of genetics services will include religious affiliation, gestational parent's age at the estimated date of delivery, socioeconomic status, number of pregnancies, and number of living children. Furthermore, decedent factors associated with uptake of postmortem genetics services will include gestational age of the pregnancy at delivery, and the number of anomalies and dysmorphic features noted on ultrasound and autopsy, respectively, if available.

(III) Explore whether there is a significant difference between documentation of clinical utility and patient education during a post-counseling session between genetics and non-genetics providers. It is hypothesized that genetics providers will document a significantly higher frequency of topics of education and counseling provided to the family compared to non-genetics providers (including a description of the significant family, medical, pregnancy, and developmental histories and pertinent test results, a review of physical exam and diagnosis, a natural history of a diagnosed condition, an explanation of inheritance, and a summary of risk assessment, if applicable).

This study seeks to provide an understanding of the gestational parent and perinatal factors that have a strong association with the decision to have a perinate undergo autopsy

in the presence or absence of a genetics work-up. In addition, given declining rates of autopsy in the US alongside continued endorsement of autopsy as the gold standard of investigation of unexplained death, this body of work will explore the link to genetic service uptake that promotes investigation in the case of perinatal death.

II. METHODS

2.1. IRB approval

This study was approved by the University of California, Irvine (UCI) Institutional Review Board (IRB) on December 1, 2021, under Expedited Review: Category 5, study 211. A letter of protocol approval by the UCI IRB can be found in Appendix A.

2.2 Retrospective chart review

The study was a chart review of perinatal demises – spontaneous abortions/intrauterine fetal demises (SAB-IUFD) and neonates that had died on or before day 28 of life – that were evaluated at the University of California, Irvine Medical Center (UCIMC) sites from November 1, 2017, to December 1, 2021. Perinatal demise records were paired with adult gestational parent records aged 18 and older for review. Gestational parents are the individuals who carried the pregnancies implicated in the prenatal or postnatal demises included in this study. Gestational parents are assumed to also be the egg donors of the pregnancies studied. SAB-IUFD encounters, being without their own medical record numbers (MRNs), were captured under their gestational parent's records. Neonatal demise newborns and their gestational parents had separate MRNs. Between November 1, 2017, and December 1, 2021, proband records were collected through UCIMC Epic electronic medical record (EMR). The start and end dates for the study were selected according to the start of the month that the UCIMC Epic EMR was implemented and the date of IRB protocol approval, respectively.

MRNs were obtained upon IRB application approval through the Department of Quality and Patient Safety at UCIMC by requesting patients that fit the above preliminary inclusion criteria. Queries for subject MRNs from the UCI Epic system were divided into three distinct search categories: spontaneous abortions and intrauterine deaths (SAB-IUFDs), delivery room deaths with linked gestational parent MRNs, and neonatal deaths on or before 28 days of life with linked maternal MRNs. SAB-IUFDs were limited to such deaths that occurred at UCIMC and excluded therapeutic abortions in the absence of an SAB or IUFD. The following ICD-10 codes were used to define the SAB-IUFD cohort: Z37.1 (single stillbirth) and O36.4 (maternal care for IUFD). Delivery room death and neonatal death UCI MRNs were obtained through the California Maternal Quality Care Collaborative. Delivery room deaths were determined by deaths of infants that occurred after 20 weeks' gestation and/or 350g birth weight and exhibited signs of life, including inhalation and expiration and/or cardiac activity. Delivery room deaths occurred within 12 hours of delivery and were never seen in the UCIMC neonatal intensive care unit (NICU). Delivery room death infants ascertained for this study were given separate MRNs from the gestational parent. Neonatal deaths occurring on or before 28 days of life included infants that died after being transferred to the UCIMC NICU. Neonatal deaths were given separate MRNs from the gestational parent. For data analysis purposes, delivery room deaths (N=20) were included in the total count of neonatal deaths. A total of 66 neonatal deaths patients and their gestational parents and 45 cases of SAB-IUFD met inclusion criteria.

Each subject was assigned a unique identifying code, linking the patient medical record numbers with newly generated non-identifying patient numbers to keep subject identifiers separate from the research information. The coded data were stored on a UCI

network computer within the secured Health Sciences network in the City Tower, Suite 800 Department of Pediatrics and at Hewitt Hall on UCI Main Campus, and the code key was stored in a separate, secure file on a UCI network computer within the secured Health Sciences network. No hard copies of coded data were collected.

2.3 Retrospective data collection in the medical records database

Patient records and postmortem documentation were reviewed, including gestational parent and fetal demographics, prenatal genetic counseling visit information, first anatomy ultrasound documentation, autopsy documentation, post-delivery genetics consult documentation, and the result of genetic testing recommended and ordered for each case. Target variables were searched by related keywords through the UCIMC Epic search bar function or by systemically reviewing scanned documents in the Media tab of the medical record. Variables were tabulated into a spreadsheet that was used for data analysis.

Gestational parent demographics such as age at estimated date of delivery (EDD), sex, primary language, ZIP code, religious affiliation, marital status, insurance type (HMO, EPO, PPO, Medicaid/Medicare/Tricare), preferred language, estimated date of delivery, compliance with 1st and 2nd-trimester genetic screening, gravidity, and the number of living children were collected. SAB-IUFD and neonatal death factors such as fetal sex, age of death/ gestation age of fetal demise, birth weight, and prenatal and postnatal genetic testing received were collected. Records that were mentioned in clinical documentation in the gestational parent's or perinatal death case's chart but were not available for the lead researcher's review were excluded from the study.

Variables collected for the first anatomy ultrasound included date of ultrasound, gestational age of the fetus at the time of ultrasound, abnormalities noted, location of ultrasound, and provider specialty providing ultrasound interpretation.

Variables for prenatal genetic counseling visits included date of session attendance, clinic location, and documentation of recommendation for medical genetics consult for infant following delivery.

Autopsy report variables collected for general autopsies included dates of autopsy procedures, dates of report submission, autopsy diagnosis, pathology case discussion, and date of results return.

Variables for the genetic consult and genetic testing recorded included the date of genetics consult, genetic testing recommended, genetic testing received, the result of genetic testing and date of results return.

A discussion of data collection methodology for key variables is as follows:

- The estimated date for delivery was documented as recorded in the admission encounter for the birth of the IUFD-SAB or neonate by the attending obstetrician or neonatologist.
- Gestational parent demographics that were subject to updates, including ZIP code and marital status, were recorded as documented in Epic during the study's data collection period (January 2022 – March 2022).
- Genetic counseling records were ascertained through the UCIMC Epic medical record. This review captured genetic counseling encounters by UCI genetic

counselors and medical geneticists at UCIMC and external records that were made available by an external referring provider.

- Autopsy records reviewed included a general autopsy of the body of the SAB-IUFD or neonatal death specimen and a neuropathological autopsy of the fetal or infant's brain. Additional examinations of products of conception or maternal organs, including examination of the placenta, fallopian tubes, and uterus in corresponding cases, were not included in data collection or analysis.
- Congenital anomalies, ultrasound soft markers, and dysmorphic features were drawn from the first anatomy ultrasound impression in the second trimester, autopsy diagnosis, autopsy case discussion, and medical geneticist consult assessment. Soft markers as indicators of aneuploidy and other conditions in pregnancy are "nonspecific, often transient, and can be readily detected during the second-trimester ultrasound" (Raniga *et al.*, 2006). While congenital anomalies (non-soft markers) have likely clinical implications, soft markers in isolation are not diagnostic for a specific clinical condition.
- Genetic testing received was categorized into karyotype, CMA, FISH, gene panel, ES, and GS.

Regarding the documentation of patient genetics education, aspects such as education of natural history, inheritance pattern education, recurrence risk, specialist referrals, additional testing, connection to resources, and psychosocial support and counseling were documented (Table 3). These points were adapted from "Guidelines for Writing Letters to Patients" from Baker *et al.* (2002), a walkthrough of writing patient letters following a genetic counseling session. Documentation for patient letters is meant to

provide a permanent record of the genetic counseling provided to a patient and thus should reflect the recommended points discussed in a results disclosure session. Documentation of genetics consults, prenatal and postnatal obstetric patient encounters, neonatology patient encounters, autopsy records, anatomy ultrasound impressions, and referring provider documents were reviewed. Review for maternal records was limited to records involving the pregnancy that concerned the SAB-IUFD or neonatal demise.

Table 3. Post-test counseling criteria (Scored out of 6)
Adapted from Baker *et al.*, 2002 & Uhlmann, 2009 from guidelines for writing a patient letter in the genetic counseling setting.

Post-test counseling criteria (Scored out of 6)
1. Description of significant family, medical, pregnancy, and developmental histories and pertinent test results 2. Review of physical exam and/ or diagnosis 3. Natural History of Condition 4. Explanation of Inheritance 5. Summary of Risk Assessment 6. Cascade/ Parental Testing Recommended

In cases in which variables of interest were not found during a thorough chart review for a given case, this information was recorded as "not documented," signifying that possible clinical action may have been taken but was not found in the patient's chart by the lead researcher.

2.4 Data analysis

Descriptive and inferential analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) Statistics version 28 (IBM SPSS Statistics for Macintosh, Armonk, NY, USA, IBM Corp). Descriptive analyses were used for demographics

of gestational parents and deceased perinates. Univariate analysis of the difference between subgroups using 2xn tables was performed using Pearson's chi-square tests or Fisher's exacts for comparisons in which at least one expected value was less than 5. A p-value of less than or equal to 0.05 was considered statistically significant.

III. RESULTS

3.1 Descriptive data

3.1.1 Demographics of gestational parents

The demographics of the study sample of gestational parents consisted of 111 adults who experienced deliveries that resulted in perinatal demise at UCIMC between November 1, 2017, and December 1, 2021, and are summarized in Table 4. The gestational parents' ages at delivery ranged from 18 to 42 years, with a mean of 32 years and a standard deviation of 5. Thirty-six gestational parents were considered of advanced maternal age for the studied pregnancy (35 years or older at the estimated date of delivery). Regarding race and ethnicity, 12 (10.8%) gestational parents identified as Asian, 7 (6.3%) identified as Black or African American, 46 (41.4%) identified as Hispanic White, 26 (23.4%) identified as non-Hispanic White, 19 (17.1%) identified as belonging to one or more racial or ethnic group, and one (0.9%) did not have a documented race or ethnicity.

Of gestational parents included in the study, 90 (81.1%) parents' preferred language was English, 17 (15.3%) patients' preferred language was Spanish, 2 (1.8%) preferred Vietnamese, 1 (0.9%) preferred Arabic, and 1 (0.9%) preferred Portuguese. Gestational parent income was estimated utilizing data from the United States Census Bureau's 2016-2020 American Community Survey was used to estimate gestational parent income. Parents lived in ZIP code regions where median family income ranged from $39,061 – $156,318, with an average median family income of $81,290 and a standard deviation of $24,139.

Gestational parents in the study declared the following religious affiliations: 2 (1.8%) were Baptist, 1 (0.9%) was Buddhist, 41 (36.9%) were Catholic, 19 (17.1%) were

Christian, 3 (2.7%) belonged to the Church of Jesus Christ of Latter-day Saints, 1 (0.9%) was Evangelical Christian, 2 (1.8%) belonged to Jehovah's Witness, 1 (0.9%) was Muslim, 1 (0.9%) was non-denominational Christian, 15 (13.5%) were non-religious, 1 (0.9%) declared "Other" for religious affiliation, and 24 (21.6%) gestational parents had unknown or missing religious affiliations or chose not to declare their affiliation.

Marital status was categorized into groups of married and non-married, including those who declared their marital status as single, having a significant other, or divorced. Fifty-eight (52.3%) patients were married, while 53 (47.7%) were non-married.

Gestational parent health insurance coverage was recorded as documented in Epic during the data collection period. Seventy-three (64.0%) gestational parents had Medicaid insurance, 28 (25.2%) had PPO insurance, 8 (7.2%) had HMO insurance, 2 (1.8%) had Tricare insurance, 1 (0.9%) had EPO insurance, and 1 (0.9%) gestational parent had no documented insurance

Including the delivery of the perinatal demise case, gestational parents' total number of pregnancies ranged from 1 to 14, with a mean of 3 and a standard deviation of 2. Similarly, including the delivery of the perinatal demise case, gestational parents' total number of living children ranged from 0 to 6, with a mean of 1 child and a standard deviation of 1.

Table 4. Demographics of gestational parents

Characteristic	Descriptive Statistics (N=111 cases)	
Demographics (Categorical)	**n**	**%**
Race/ ethnicity		
Asian	12	10.8
Black or African American	7	6.3
Hispanic White	46	41.4
Non-Hispanic White	26	23.4
One or more	19	17.1
Unknown/ Missing/ Prefers not to declare	1	0.9
Preferred Language		
English	90	81.1
Spanish	17	15.3
Vietnamese	2	1.8
Arabic	1	0.9
Portuguese	1	0.9
Marital Status		
Married	58	52.3
Non-Married	53	47.7
Religious Affiliation		
Baptist	2	1.8
Buddhist	1	0.9
Catholic	41	36.9
Christian	19	17.1
The Church of Jesus Christ of Latter-day Saints	3	2.7
Evangelical	1	0.9
Jehovah's Witness	2	1.8
Muslim	1	0.9
Non-Denominational Christian	1	0.9
Non-Religious	15	13.5
Other	1	0.9
Unknown/ Missing/ Prefers not to declare	24	21.6

Table 4 (Continued). Demographics of gestational parents

Insurance Type		
Medicaid	71	64.0
PPO	28	25.2
HMO	8	7.2
Tricare	2	1.8
EPO	1	0.9
Not Documented	1	0.9
Demographics (Continuous)		
Age at delivery, years		
Mean (S.D.)		32 (5)
Median		32
Range		18-42
Total number of pregnancies		
Mean (S.D.)		3 (2)
Median		3
Range		1-14
Total Number of Living Children		
Mean (S.D.)		1 (1)
Median		1
Range		0-6
Median family income by ZIP code, dollars		
Mean (S.D.)		81,290 (24,139)
Median		75,219
Range		39,061 – 156,318

3.1.2 Demographics of perinates

The study sample of perinates included 111 spontaneous abortions and intrauterine fetal demises (SAB-IUFDs) and neonatal deaths, summarized in Table 5. Within the perinatal demise sample, there were 66 (59.5%) demises categorized as SAB-IUFDs and 45 (40.5%) categorized as neonatal deaths. Perinatal sex was documented in 108 cases, with 57 males and 51 females. In 11 cases (9.9%), the demise was a part of a multiple gestation (i.e., a twin or triplet pregnancy). One multiple gestation was a triplet pregnancy conceived via in-vitro fertilization. The mean gestational age at delivery was 27 weeks with a standard deviation of 6 and a range of 20 to 41 weeks' gestation. Birth weight was documented in 93 cases (83.8%) with a mean weight of 1170.26 grams, a standard deviation of 834.50, and a range of 190 to 4320 grams.

Table 5. Demographics of perinates

Characteristic	Descriptive Statistics (N=111 cases)	
Demographics (Categorical)	**n**	**%**
Demise Type		
SAB-IUFD	66	59.5
Neonatal Deaths	45	40.5
Sex		
Male	57	51.4
Female	51	45.9
Not Documented	3	2.7
Was Demise a Part of a Multiple Gestation?		
Yes	11	9.9
No	100	90.1
Demographics (Continuous)		
Gestational Age, weeks		
Mean (S.D.)	27 (6)	
Median	26	
Range	20-41	
Birth Weight, grams		
Mean (S.D.)	1310.08 (1043.70)	
Median	832.50	
Range	190-4320	

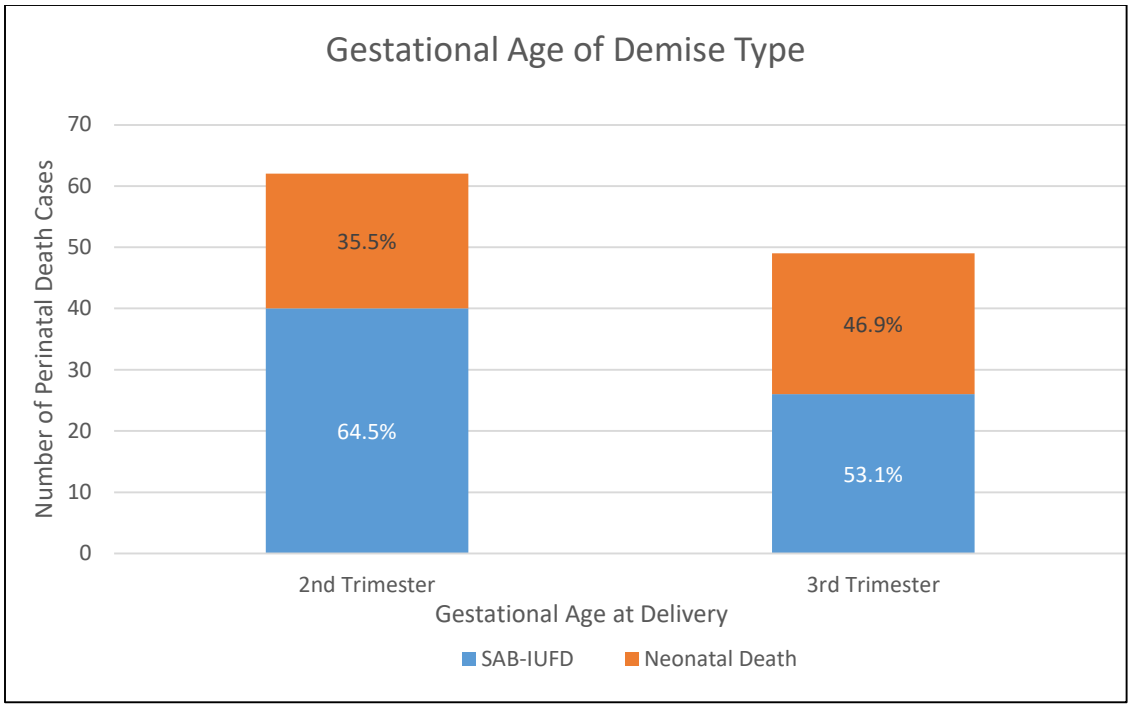

Figure 1. Comparison of gestation age of delivery with demise type (N=111). Gestational ages at delivery for perinatal demise cases were categorized by the second trimester (20 weeks 0 days to 27 weeks 6 days) or third trimester (28 weeks 0 days onward). There was no statistically significant difference between demise type and gestational age at delivery (p=0.222).

3.1.3 Characteristics of anatomy ultrasound impression

In the absence of other indications for ultrasound, the first anatomy ultrasound during pregnancy is recommended between 18-22 weeks' gestation (Practice bulletin no. 175: Ultrasound in pregnancy, 2016). Eighty perinates had the first anatomy ultrasound records documented in the UCI Epic medical record, with characteristics documented in Table 6. The range of administration of the first anatomy ultrasound ranged between 15 weeks 2 days and 29 weeks 2 days. Forty-two first anatomy ultrasounds were administered in the first trimester, 36 in the second, and 2 in the third. Ultrasound anomalies were categorized by system, including the respiratory, cardiovascular/ lymphatic, gastrointestinal, reticuloendothelial, genitourinary, musculoskeletal/ craniofacial, endocrine, and central nervous systems. Cases that had anomalies detected in a single body system were divided into groups according to the system affected. Cases with more than one anomalous system were categorized as having multiple system anomalies. Cases that had only soft markers detected were counted separately. Cases that had no observed anomalies on the first anatomy ultrasound were categorized as "No anomalies detected." Thirty-one (38.8%) perinatal cases had anomalies observed in multiple body systems, while 22 (31.2%) had anomalies affecting a single body system. In perinates with single system anomalies, body systems with anomalies appreciated included the genitourinary system (9), the cardiovascular system (5), the craniofacial/ development field (3), the central nervous system (3), and the gastrointestinal system (2), as depicted in Table 6 and Figure 2. No perinatal case was found to have anomalies in the respiratory, reticuloendothelial, or endocrine systems. Regarding the presence of soft markers, 4 cases only had soft markers detected on ultrasound. These included one case with a two-vessel

cord, two cases with an echogenic intracardiac focus only, and one case with both an echogenic intracardiac focus and choroid plexus cyst. Twenty (25%) cases had at least one soft marker and one non-soft marker anomaly detected. Thirty-three (41.3%) cases had only non-soft marker anomalies detected (Figure 3). Forty anatomy ultrasounds were conducted at UCI Medical Center, while 40 were conducted at non-UCI ultrasound clinics. In 66 cases, the ultrasound was interpreted by a maternal-fetal medicine specialist, while in 14 cases, the ultrasound was interpreted by a non-maternal fetal medicine obstetrician.

Table 6. Anatomy ultrasound (U/S) demographics

Characteristic	N	n	%
Received First Anatomy U/S	111		
Yes		80	72.1
No/ Not Documented		31	27.9
Gestation Age at First Anatomy U/S	80		
1st Trimester		42	52.5
2nd Trimester		36	85.7
3rd Trimester		2	4.8
Number of Ultrasound System Anomalies	80		
None		23	28.8
Soft markers only		4	5.0
Anomalies in a single system		22	31.2
Anomalies in multiple systems		31	38.8
Single System Anomalies	22		
Respiratory System		0	0.0
Cardiovascular/ Lymphatic System		5	22.7
Gastrointestinal System		2	9.1
Reticuloendothelial System		0	0.0
Genitourinary System		9	40.9
Musculoskeletal/ Craniofacial System		3	13.6
Endocrine System		0	0.0
Central Nervous System		3	13.6
Presence of Soft Markers	80		
No anomalies detected		23	28.8
Soft markers only		4	5.0
Soft makers and non-soft markers		20	25.0
Only non-soft markers		33	41.3
Ultrasound Clinic Location	80		
UCIMC		40	50.0
External		40	50.0
Ultrasound Reading Physician	80		
MFM		66	82.5
Non-MFM		14	17.5

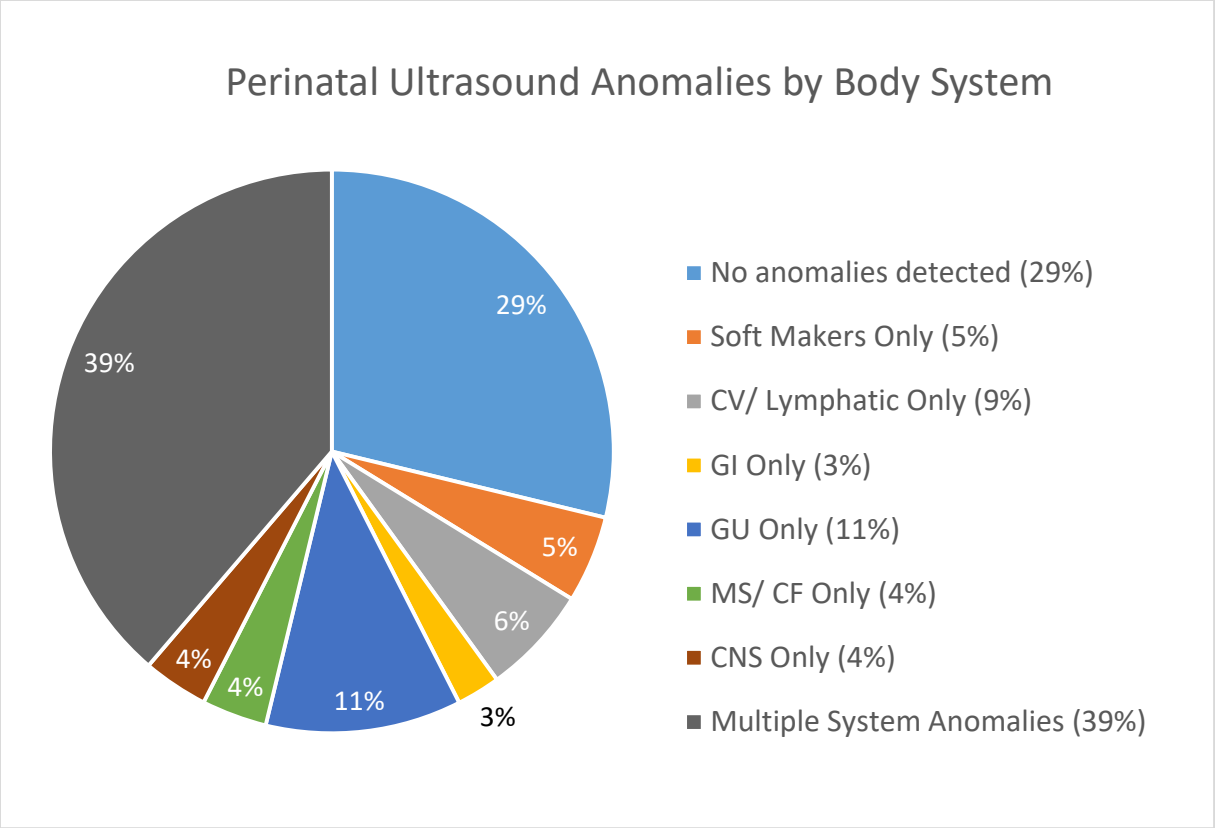

Figure 2. Perinatal ultrasound anomalies by body system (N=80). Depicted are first anatomy ultrasound anomalies categorized by the number of body systems affected. Almost half of the cases (39%) that received a documented anatomy ultrasound had anomalies in multiple body systems. Of cases that had anomalies in a single body system, most cases had anomalies only affecting the genitourinary system (11%). CNS = Central nervous system, CV = Cardiovascular; GI = Gastrointestinal; GU = Genitourinary; MS/CF = Musculoskeletal/ Craniofacial

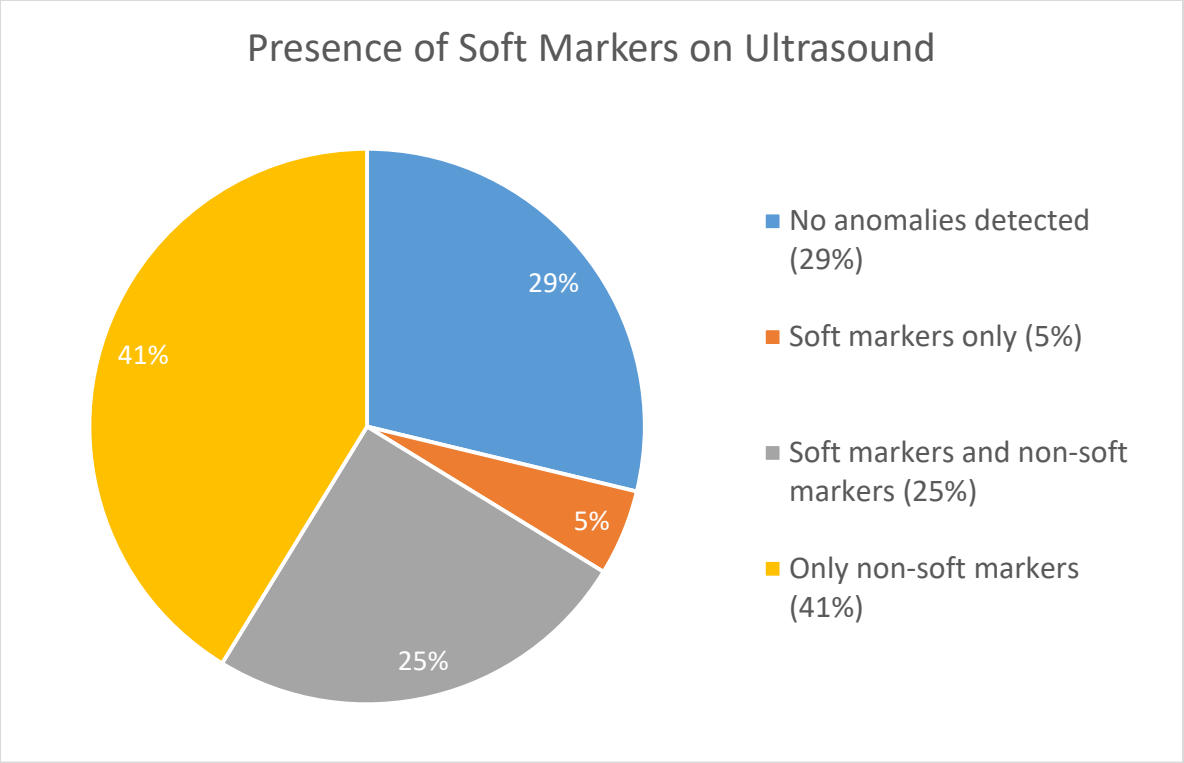

Figure 3. Presence of soft markers on ultrasound (N=80). A minority of cases that had a documented first anatomy ultrasound had only soft markers detected (5%). A majority (41%) had only non-soft markers observed on ultrasound, while 25% had at least one soft marker and at least one non-soft marker anomaly detected.

3.1.4 Clinical characteristics of prenatal genetic counseling and postnatal genetics consult

In-clinic genetics services were documented in terms of attendance prenatal or postnatally in Table 7. Forty-six (41.4%) perinatal cases had documented referrals to prenatal genetics, while 37 (33.3%) attended a genetic counseling appointment prenatally. Of the 37 cases seen in genetics prenatally, 26 cases (70.2%) were seen at a UCI-affiliated site, while 11 (30.0%) patients were seen at a non-UCI facility. Twelve cases were recommended for medical genetics consult following delivery; all were referred for an abnormal ultrasound. Of the twelve referred for genetics consult following delivery in a prenatal genetic counseling appointment, 6 (50%) were seen post-delivery by a medical geneticist. In one case, prenatal karyotype was negative, and Medicaid insurance denied reflex to CMA. In one case, the gestational parent declined further genetic testing and genetics services. In four cases with an abnormal result received prenatally (Trisomy 13) or postnatally (sex discrepancy on CMA, FGFR3-related thanatophoric dysplasia, and COL2A1-related disorder), results were discussed with a genetic counselor (Table 8).

Overall, twenty-eight (25.2%) perinates were referred for genetics consult post-delivery, with 19 (17.1%) receiving genetics consult. The 9 (8.1%) cases that were referred for post-delivery genetics consult with physical examination but did not attend the visit are summarized in Table 9. Of the 9 that were not seen for post-delivery genetics consult following referral, 5 had abnormal genetic testing results, while 4 had normal genetic testing results. Of the 5 that received abnormal results, all had documented results returns and were referred to genetics following results return. However, only 1 case was seen in genetics at UCI. Of the 4 that were not seen in genetics following referral, one gestational parent declined genetics follow-up, while 3 had no documented follow-up.

Forty-seven (42.3%) perinatal demise cases received a dysmorphology exam by either a medical geneticist, pathologist, obstetrician, or neonatologist. Fifteen of the 47 (31.9%) received a dysmorphology exam by a medical geneticist. In 60 (54.0%) cases, the perinate received at least one type of diagnostic genetic testing prenatally or postnatally, including karyotype, CMA, FISH assay, single or multi-gene panel, or exome sequencing. No perinatal case was documented to have received genome sequencing. Between the 60 perinates that received genetic testing, 88 total genetic tests were recommended. Among those 60 perinates, 78 total genetic tests were received. Recommendation and reception rate by genetic test type is displayed in Table 10. Of the 60 perinates that received genetic testing, 24 (40.0%) received a diagnostic result (pathogenic or likely pathogenic result), 4 (6.7%) received a variant of uncertain significance, 31 (51.7%) received a negative result, and 1 (1.7%) received a result of sex discrepancy of female sex detected in a male fetus. In this case, maternal cell contamination was ruled out, suggesting the possibility of chimerism from an undetected cotwin demise (Table 11 and Figure 4). Of the 24 perinates that received a diagnostic result, 11 (45.8%) had a monogenic disorder, 10 (41.7%) had a chromosomal aneuploidy, 2 (8.3%) had a copy number variant-implicated disorder, and 1 (4.1%) had genome-wide uniparental isodisomy (Table 12). Appendices B and C depict tables of the genetic diagnostic results for fetal deaths and neonatal deaths, respectively, including ultrasound findings, autopsy findings, dysmorphology exam findings, pre- and postnatal genetics involvement, genetic testing received, diagnostic results, and whether the result explains the anomalies observed in the prenatal and postnatal examination. A flowchart of perinatal death cases that received post-delivery genetics consults, autopsy, and genetic testing is depicted in Appendix B.

Table 7. Demographics of cases referred for prenatal and postnatal genetics evaluations.

Characteristic	N	n	%
Referred to genetics prenatally?	111		
Yes		46	41.4
No		65	58.5
Attended prenatal genetics visit?	111		
Yes		37	33.3
No		74	66.7
Prenatal genetics clinic affiliation	37		
UCIMC		26	70.3
Non-UCI		11	29.7
Recommended genetics consult after delivery by a genetic counselor?	37		
Yes		12	32.4
No		25	67.6
Referred to genetics consult postdelivery?	111		
Yes		28	25.2
No		83	74.8
Received postdelivery genetics consult?	111		
Yes		19	17.1
No		92	82.9
Medical geneticists involved in dysmorphology exam?	111		
Yes, medical geneticist involved		15	13.5
No, medical geneticist not involved		32	28.8
No, did not receive dysmorphology exam		64	57.7
Received at least one genetic test prenatally and/or postnatally?	111		
Yes		60	54.1
No		51	45.9

Table 8. Summary of perinatal cases that were not seen for medical geneticist post-delivery consult and physical examination following prenatal genetic counselor recommendation (N=6).

Referral Indication for Prenatal GC	Genetic Testing (Recommended by)	Genetic Testing Received	Follow-Up
U/S finding of multiple fetal anomalies	Normal karyotype; Medicaid insurance denied reflex to CMA (Obstetrics)	Prenatally	Result returned by GC
U/S finding of hydrops	None, declined	None	N/A
AMA, U/S findings of anhydramnios, scoliosis, and clubfoot	Sex discrepancy identified by CMA; (Genetics)	Following delivery	Result returned by GC; gestational parent sample to r/o MCC
U/S findings of micromelia, talipes, and pulmonary hypoplasia	Thanatophoric dysplasia by panel; (Genetics)	Following delivery	Result returned by GC
Suspected fetal skeletal dysplasia	COL2A1-related disorder by panel (Genetics)	Following delivery	Result returned by GC
U/S finding of fetal abnormality, AMA	Trisomy 21 by CMA (External)	Prenatally	Result returned by GC

GC = Genetic counselor; MCC = maternal cell contamination; R/o = rule out; U/S = ultrasound

Table 9. Summary of perinatal cases that did not attend post-delivery consult with medical geneticist with dysmorphology exam after being referred for consult following delivery (N=9)

Referral Indication for Genetics Consult	Genetic Testing (Recommended by)	Genetic Testing Received	Follow-Up	Referred to Genetics Post-Result?	Seen in Genetics at UCI Post-Referral?
IUGR	Normal CMA (Obstetrics)	At Delivery	Result returned by OB	No	N/A
IUFD	Mosaic Trisomy 13 by SNP CMA (Obstetrics)	At Delivery	Result returned by OB-GYN, referred to GC	Yes	No
IUFD	16p11.2 duplication syndrome by CMA (Obstetrics)	At Delivery	Result returned by nurse practitioner, referral to GC	Yes	No
Pregnancy loss at 20 weeks, triploidy	Triploidy by CMA (Genetics, Obstetrics)[a]	At Delivery	Results returned by nurse practitioner, referred to GC	Yes	No

a = Offered prenatally by a genetic counselor, but gestational parent elected to test products of conception after delivery. Obstetrics recommended CMA testing again after delivery. CMA = Chromosomal microarray; GC = Genetic counselor; IUFD = Intrauterine fetal demise; IUGR = Intrauterine growth restriction; PPV = post-partum visit; SNP = Single nucleotide polymorphism; VUS = Variant of uncertain significance

Table 9 (Continued). Summary of perinatal cases that did not attend post-delivery consult with medical geneticist with dysmorphology exam after being referred for consult (N=9)

Referral Indication for Genetics Consult	Genetic Testing (Recommended by)	Genetic Testing Received	Follow-Up	Referred to Genetics Post-Result?	Seen in Genetics at UCI Post-Referral?
Severe hydrops	VUS 11p15.4 deletion by CMA; VUS SPTA1 c.5572C>G p.Leu1858Val by panel; Pathogenic HBA1/HBA2 alpha-globin gene locus: homozygous 20kb --SEA Deletion by panel (Genetics)[b]	At delivery	Genetics phone consult only; seen by neonatology for results returned, declined GC	Yes	No, declined
Tetralogy of Fallot, hydrops	Normal CMA, postnatal (Pediatric cardiology)	At Delivery	Not documented	No	N/A
Suspected diagnosis of skeletal dysplasia	FGFR3 c.746C>G p.Ser249Cys [pathogenic], FGFR3 c.2417C>T p.Thr806Met [VUS] (Genetics)[c]	At delivery	Results returned by genetic counselors	Yes	Yes
Megacystis	Normal CMA (Neonatology)	Prenatally	Results returned by neonatology	No	N/A
Fetal cardiac anomaly	Normal CMA (Neonatology)	At delivery	PPV not attended	No	N/A

b = recommended by phone consult with medical geneticist; c = offered prenatally by a genetic counselor, but gestational parent elected to test neonate after delivery.

Table 10. Rate of cases that received genetic testing after recommendation

Genetic Testing Type	Received N = 78	Recommended N=88	Test Reception Rate (%)
Karyotype	16	18	88.9
CMA	48	50	96.0
FISH*	2	3	66.7
Single gene/ Multigene panel	11	14	78.6
Exome sequencing	1	3	33.3

*Recommended for concerns of aneuploidy

Table 11. Result of genetic testing

Result of Genetic Testing Cases That Received Genetic Testing, N=60	**n**	**%**
Positive	24	40.0
Variant of Uncertain Significance	4	6.7
Sex discrepancy	1	1.7
Negative	31	51.7

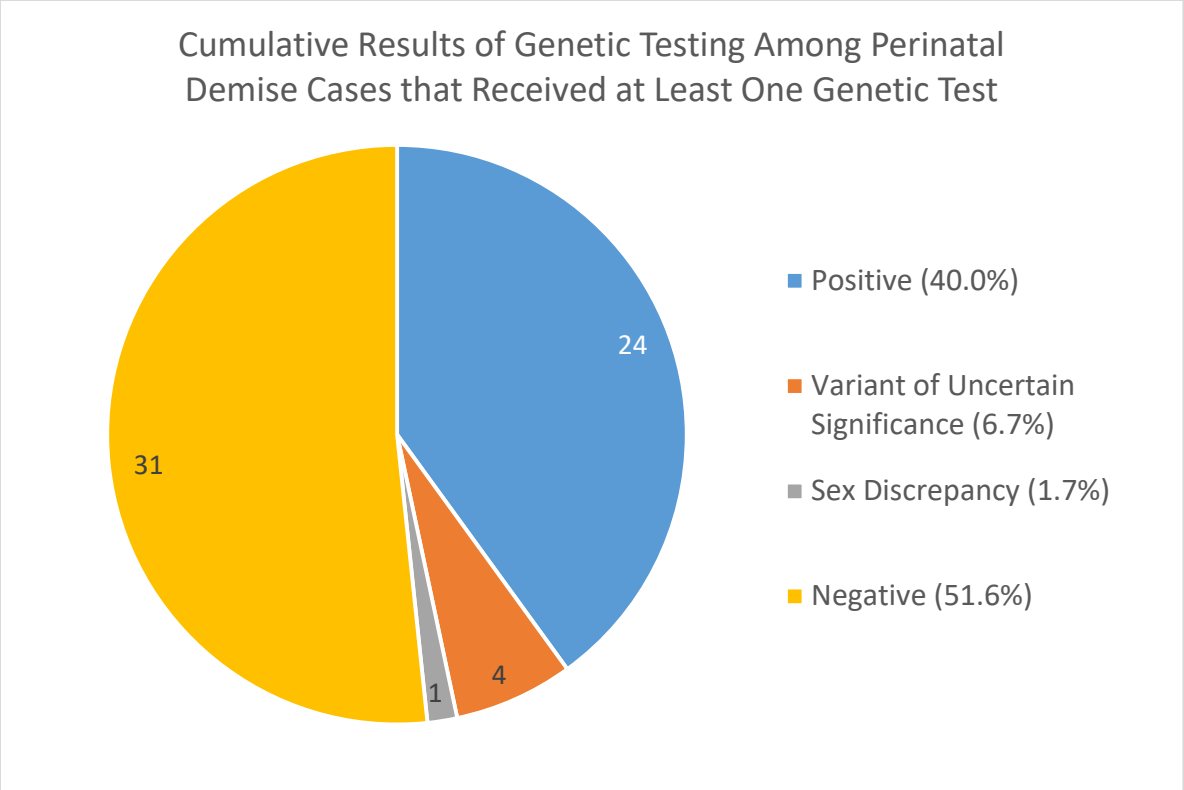

Figure 4. Cumulative results of genetic testing among perinatal demise cases that received at least one genetic test. Out of 111 perinatal demise cases, 60 received genetic testing. Twenty-three received a positive result, 4 received a variant of uncertain significance, 1 case had a CMA with DNA from cord blood that resulted in a sex discrepancy (maternal cell contamination ruled out) thought to be possible chimerism from a cotwin demise, and 31 cases received entirely negative results.

Table 12. Cases that received genetic diagnosis

Genetic Diagnostic Category for Pathogenic/ Likely Pathogenic Results	Number of Perinatal Demise Cases N=24	%	Genetic Diagnostic Testing Type
Chromosomal Conditions	**n=10**	**41.7**	
Trisomy 13	1		Karyotype
Mosaic Trisomy 13	1		SNP CMA
Trisomy 18	3		Karyotype, FISH
Trisomy 21	3		Karyotype
Triple X Syndrome	1		Karyotype
Triploidy	1		CMA
Copy Number Variant Disorders	**n=2**	**8.3**	
16p11.2 Duplication Syndrome	1		CMA
16p11.2 Deletion Syndrome	1		CMA
Uniparental Disomy Disorders	**n=1**	**4.1**	
Beckwith-Wiedemann Syndrome	1		SNP CMA[a]
Monogenic Conditions	**n=11**	**45.8**	
Autosomal Recessive Polycystic Kidney Disease	2		Panel
COL2A1-Related Disorder	1		Panel
Hemoglobin Barts Syndrome	1		NBS[b], Panel
Nager Syndrome	1		CMA
Noonan-Spectrum Syndrome	2		Panel, ES
Osteogenesis Imperfecta	1		Panel
Syndromic Microphthalmia	1		Panel
Thanatophoric Dysplasia	2		Panel

a = CMA revealed genome-wide uniparental isodisomy mosaicism. Beckwith-Wiedemann Syndrome and Russell Silver Syndrome Methylation by MLPA was normal. Assumption of BWS diagnosis based on clinical findings; **b** = One case of Hemoglobin Barts Syndrome was diagnosed initially by the California Newborn Screening Program (NBS) and confirmed by an alpha thalassemia panel. CMA = Chromosomal microarray; ES = Exome sequencing; FISH = Fluorescence in situ hybridization.

3.1.5 Characteristics of genetic testing results return

In 60 cases of perinatal demise that underwent genetic testing, 35 (58.3%) were documented as discussed with the gestational parent. In the 29 cases of abnormal results, 22 (75.9%) had a result return documented. Three cases with VUS results of testing recommended by obstetrics and neonatology did not have documented returns. Three cases with genetic testing recommended by a geneticist (Trisomy 21, 16p.11.2 deletion syndrome, and thanatophoric dysplasia) had no documented results returned. In the case of the neonate with Trisomy 21, the gestational parent was late to her postpartum follow-up visit and left early. She declined additional follow-up at UCI in favor of seeing her non-UCI-affiliated obstetrician. In the cases of the neonate with 16p11.2 deletion syndrome, an attempt was made to reach the patient by phone. Another case with a prenatal diagnosis of trisomy 21 was made at a non-UCI-affiliated site. The results return was not available for review.

3.1.6 Clinical characteristics of perinatal autopsy

Of the 111 cases, autopsy consenting was documented in 97 (87.4%) cases of perinatal demise. Thirty-seven (33.3%) underwent autopsy while 62 (55.9%) were documented to have declined autopsy that was offered. There were 12 (10.8%) cases in which a final decision for autopsy was not documented and with no autopsy on record. Of the 37 cases that underwent autopsy, 5 (13.5%) had no anomalous systems detected on autopsy, 6 (16.2%) had 1-3 anomalous systems detected on autopsy, 16 (43.2%) had 4-5 anomalous systems detected, and 10 (27.0%) had six or more anomalous systems detected (Table 13).

Submission attributes for provisional and final autopsy reports were documented. Dates of submission were recorded from the EMR of the gestational parent of SAB-IUFDs or the neonatal death. The mean turnaround time for provisional autopsy reports from the time of autopsy to submission to the EMR was 32.22 days with a median of 7 days, a standard deviation of 46.92 with a range of 1-190 days. The mean turnaround time for final autopsy reports from the time of autopsy to submission to the EMR was 118.14 days, a median of 121 days, and a standard deviation of 78.53 days with a range of 8-329 days. In all 37 cases, preliminary autopsy findings were attempted to be discussed with the ordering physician. A figure of autopsy report turnaround time is documented in Appendix E.

Table 13. Autopsy demographics

Characteristics	N	n	%
Received autopsy consent	111		
Yes		97	87.4
No		2	1.8
Not Documented		12	10.8
Outcome of autopsy consent	111		
Accepted		37	33.3
Declined		72	64.9
Not Documented		2	1.8
Number of systems affected by anomalies on autopsy	37		
0		5	13.5
1-3		6	16.2
4-5		16	43.2
>=6		10	27.0

3.2 Univariate analyses

3.2.1 Univariate analysis of factors that may predict uptake of fetal or infant autopsy

Cases of perinatal demise that received autopsy and did not receive autopsy were compared based on their fetal and infant demographics and gestational parent demographics using Chi-Square tests for association. Two-sided Fisher's exact tests were used when at least one expected cross table value was less than 5. Gestational ages at delivery for perinatal demise cases were categorized by the second trimester (20 weeks 0 days to 27 weeks 6 days) or third trimester (28 weeks 0 days onward). Anatomy ultrasound anomalies were categorized as to whether 0, 1-3, 4-5, or 6 or more anomalous systems were detected. Dates of delivery or birth for perinatal demise cases were categorized by whether they occurred before March 11, 2020, the date the World Health Organization declared the novel coronavirus (COVID-19) outbreak a global pandemic. Due to the small number of individual racial and ethnic groups in the study, race and ethnicity were categorized into three groups: White Non-Hispanic, Hispanic, and Other. The "Other" category included individuals who identified as Asian, Black or African American, and multiracial. Similarly, due to the small size of preferred language groups, languages were categorized into English as a preferred language or other preferred languages, which included Spanish, Vietnamese, Arabic, and Portuguese. Median income by ZIP code was grouped into quartiles (less than $64,876, $64,877-$75,218, $75,219-$96,737, and greater than $96,738. Whether a gestational parent of a demise case was of advanced maternal age was determined by calculating their age was 35 and over (considered advanced maternal age) or under 35 at the estimated date of delivery for the pregnancy. Religious affiliation for gestational parents was categorized into whether gestational parents identified as

Catholic, other Christian (which included Christian, restorationist Christian denominations, and Protestant Christian denominations), other non-Christian, and non-religious (which included Agnostic and no religious affiliation). Whether the gestational parent's religious affiliation was unknown, missing, or declined to document was listed under a single category. It should be noted that the documentation of religious affiliation as Christian versus non-Christian is an analytical decision owing to the larger sample size of gestational parents declaring a Christian religious affiliation in comparison to other religious affiliations. The total number of pregnancies for the gestational parent following the delivery of the perinatal demise was categorized into one pregnancy (that of the demise) or two or more pregnancies. Similarly, the total number of living children was categorized into whether the gestational parent had no living children or one living child or if they had two or more living children. Insurance providers were divided into private insurance providers (PPO, HMO, and EPO) and government insurance providers (Medicaid and Tricare). Whether the pregnancy was seen prenatally by a genetics provider was documented.

A significant relationship was identified between autopsy uptake and demise type ($p=0.001$). Regarding perinatal demographics, the relationship between autopsy uptake and fetal sex, gestational age at delivery, number of systems with anomalies detected on ultrasound, and whether the date of delivery was before or during the COVID-19 pandemic were not statistically significant. Regarding gestational parent demographics, the relationship between autopsy uptake and race/ethnicity, preferred language, estimated median income by ZIP code, whether the gestational parent was of advanced maternal age at delivery, marital status, religious affiliation, total pregnancies, total living children,

insurance provider category, insurance provider type, or whether the pregnancy was seen in genetics prenatally were not statistically significant. These results are shown in Table 14. Additionally, no significant difference was found between demise type and gestational age of perinatal demise cases (p=0.222) (Table 15).

Table 14. Comparison of fetal/infant and gestational parent demographic characteristics between perinatal demise subjects who received autopsy and those who did not.

Factor	Received Autopsy					
Fetal/ Infant Demographics	**N**	**Yes n (%)**	**No n (%)**	**χ2**	**df**	**p-value**
Demise type	111			10.764	1	0.001
SAB-IUFD		14 (21.1%)	52 (78.8%)			
Neonatal death		23 (51.1%)	22 (48.9%)			
Sex	108			0.046	1	0.830
Male		19 (33.3%)	38 (66.7%)			
Female		18 (35.3%)	33 (64.7%)			
Gestational age at delivery	111			2.211	1	0.137
Second trimester		17 (27.4%)	45 (72.6%)			
Third trimester		20 (40.8%)	29 (59.2%)			
Ultrasound anomalies	76			2.580	2	0.275
None detected		8 (34,8%)	15 (65.2%)			
Single system		7 (31.8%)	15 (68.2%)			
Multiple systems		16 (51.6%)	15 (48.4%)			
DOB before or during COVID-19 pandemic	111			0.168	1	0.682
Pre-pandemic		23 (34.8%)	43 (65.2%)			
During pandemic		14 (31.1%)	31 (68.9%)			
Gestational Parent Demographics	**N**	**Yes n (%)**	**No n (%)**	**χ2**	**df**	**p-value**
Race/ ethnicity	110			0.673	2	0.714
White Non-Hispanic		10 (38.5%)	16 (61.5%)			
Hispanic		16 (34.8%)	30 (65.2%)			
Other		11 (28.9%)	27 (71.1%)			
Preferred language	111			1.057	2	0.304
English		32 (35.5%)	58 (64.4%)			
Other		5 (23.8%)	16 (76.2%)			

Table 14 (Continued). Comparison of fetal/infant and gestational parent demographic characteristics between perinatal demise subjects who received autopsy and those who did not.

Factor	Received Autopsy					
Gestational Parent Demographics	**N**	**Yes n (%)**	**No n (%)**	**$\chi 2$**	**df**	**p-value**
Median income by ZIP code	111			2.516	3	0.472
$39,061-$64,876		8 (32.0%)	17 (68.0%)			
$64,877-$75,218		6 (21.4%)	22 (78.6%)			
$75,219-$96,737		12 (38.7%)	19 (61.3%)			
$96,738-$156,318		10 (38.5%)	16 (61.5%)			
AMA at EDD	111			0.185	1	0.667
Yes		11 (30.6%)	25 (69.4%)			
No		26 (34.7%)	49 (65.3%)			
Marital status				0.885	1	0.347
Married	111	17 (29.3%)	41 (70.7%)			
Non-married		20 (37.7%)	33 (62.3%)			
Religion declared	111			0.019	1	0.889
Yes		23 (32.9%)	47 (67.1%)			
No		14 (34.1%)	27 (65.8%)			
Total Pregnancies	111			0.673	1	0.412
1-2		17 (37.8%)	28 (62.2%)			
>3		20 (30.3%)	46 (69.7%)			
Total living children	108			1.987	1	0.159
0-1		26 (39.4%)	40 (60.6%)			
>2		11 (26.2%)	31 (73.8%)			
Insurance provider category	110			0.036	1	0.849
Private		12 (32.4%)	25 (67.6%)			
Government		25 (34.2%)	48 (65.8%)			
Insurance provider type	89			0.569	1	0.451
PPO		11 (39.3%)	17 (60.7%)			
Medicaid		19 (31.1%)	42 (68.9%)			

Table 14 (Continued). Comparison of fetal/infant and gestational parent demographic characteristics between perinatal demise subjects who received autopsy and those who did not.

Factor	Received Autopsy					
Gestational Parent Demographics	**N**	**Yes n (%)**	**No n (%)**	**$\chi 2$**	**df**	**p-value**
Seen in genetics prenatally	111			0.081	1	0.776
Yes		13 (35.1%)	24 (64.9%)			
No		24 (32.4%)	50 (67.6%)			

Table 15. Comparison of perinatal demise type and gestational age at delivery.

Factor	Gestational Age					
Fetal/ Infant Demographics	**N**	**2nd Trimester n (%)**	**3rd Trimester n (%)**	**$\chi 2$**	**df**	**p-value**
Demise type	111			1.490	1	0.222
SAB-IUFD		40 (60.6%)	26 (39.4%)			
Neonatal death		22 (48.9%)	23 (51.1%)			

3.2.2 Univariate analysis of factors that may predict referral to genetics consult post-delivery

Perinatal death and gestational parent factors, as discussed in sections 3.1.1, 3.1.2, and 3.1.3., were compared with the reception of genetics consult services after delivery of the perinatal demise case. Significant relationships were found between uptake of genetics consult after delivery and demise type ($p<0.001$), gestational age at delivery ($p<0.001$), number of systems in which structural anomalies were detected on anatomy ultrasound ($p=0.021$), and preferred gestational parent language ($p=0.021$). No statistically significant relationship was found between the remaining factors, including whether the pregnancy had been seen in prenatal genetics and the evaluation by genetics consult following delivery. Results are summarized in Table 16.

Table 16. Comparison of fetal/infant and gestational parent demographic characteristics between perinatal demise subjects who received post-delivery genetics consult and those who did not.

Factor	Received Genetics Consult Post-Delivery					
Fetal/ Infant Demographics	**N**	**Yes n (%)**	**No n (%)**	**$\chi 2$**	**df**	**p-value**
Demise type	111			14.028	1	<0.001
SAB-IUFD		4 (6.1%)	62 (93.9%)			
Neonatal death		15 (33.3%)	30 (66.7%)			
Sex	108			0.997	1	0.318
Male		12 (78.9%)	45 (21.1%)			
Female		7 (13.7%)	44 (86.3%)			
Gestational age at delivery	111			11.261	1	<0.001
2nd trimester		4 (6.5%)	58 (93.5%)			
3rd trimester		15 (29.2%)	34 (70.8%)			
Ultrasound anomalies	76			8.209	2	0.020[a]
None detected		2 (8.7%)	21 (91.3%)			
Single system		3 (13.6%)	19 (86.4%)			
Multiple systems		12 (38.7%)	19 (61.3%)			
Soft marker anomalies only	57			1.536	1	0.564 [a]
Yes		0	4 (100.0%)			
No		15 (28.3%)	38 (71.7%)			
DOB before or during COVID-19 pandemic	111			0.764	1	0.382
Pre-pandemic		13 (19.7%)	53 (80.3%)			
During pandemic		6 (13.3%)	39 (86.7%)			

[a] 2-sided Fisher's Exact Test

Table 16 (Continued). Comparison of fetal/infant and gestational parent demographic characteristics between perinatal demise subjects who received post-delivery genetics consult and those who did not.

Factor	Received Genetics Consult Post-Delivery					
Gestational Parent Demographics	**N**	**Yes n (%)**	**No n (%)**	**$\chi 2$**	**df**	**p-value**
Race/ ethnicity	110			1.224	2	0.497[a]
White Non-Hispanic		6 (23.1%)	20 (76.9%)			
Hispanic		6 (13.0%)	40 (87.0%)			
Other		7 (18.4%)	31 (81.6%)			
Preferred language	111			5.349	1	0.021[a]
English		19 (21.1%)	71 (78.9%)			
Other		0	21 (100.0%)			
Median income by ZIP code	111			0.563	3	0.905
$39,061-$64,876		5 (19.2%)	21 (80.8%)			
$64,877-$75,218		5 (17.9%)	23 (82.1%)			
$75,219-$96,737		4 (12.9%)	27 (87.1%)			
$96,738-$156,318		5 (19.2%)	21 (80.8%)			
AMA at EDD	111			0.203	1	0.652
Yes		7 (19.4%)	29 (80.6%)			
No		12 (16.0%)	63 (84.0%)			
Marital status	111			1.093	1	0.296
Married		12 (20.7%)	46 (79.1%)			
Non-married		7 (13.2%)	46 (86.8%)			
Religion declared	111			2.483	1	0.115
Yes		15 (21.4%)	55 (78.6%)			
No		7 (17.1%)	34 (82.9%)			
Total pregnancies	111			0.443	1	0.506
1-2		12 (18.5%)	53 (81.5%)			
>3		7 (15.2%)	39 (84.8%)			

[a] 2-sided Fisher's Exact Test

Table 16 (Continued). Comparison of fetal/infant and gestational parent demographic characteristics between perinatal demise subjects who received post-delivery genetics consult and those who did not.

Factor	Received Genetics Consult Post-Delivery					
Gestational Parent Demographics	**N**	**Yes n (%)**	**No n (%)**	**χ2**	**df**	**p-value**
Total living children	108			0.281	1	0.596
0-1		12 (18.2%)	54 (81.8%)			
>2		6 (14.3%)	36 (85.7%)			
Insurance provider category	110			0.106	1	0.745
Private		7 (18.9%)	30 (81.2%)			
Government		12 (16.4%)	61 (83.6%)			
Insurance provider type	89			1.366	1	0.242
PPO		7 (25.0%)	21 (25.0%)			
Medicaid		9 (14.8%)	52 (85.2%)			
Seen in genetics prenatally	111			2.032	1	0.154
Yes		9 (24.3%)	28 (75.7%)			
No		10 (13.5%)	64 (86.5%)			

[a] 2-sided Fisher's Exact Test

3.2.3 Univariate analysis of factors that may predict reception of genetic testing

Perinatal death and gestational parent factors as outlined in sections 3.1.1, 3.1.2, and 3.1.3. were compared with the reception of pre- and postnatal genetic testing. Significant relationships were found between uptake of pre- and postnatal genetic testing and gestational age at delivery ($p<0.001$), number of ultrasound anomalies by body system ($p<0.001$), whether autopsy had been performed ($p<0.001$), number of autopsy anomalies observed by body system, gestational age at delivery ($p<0.001$), whether a genetics specialist was involved in dysmorphology exam ($p=0.042$), whether the pregnancy was

seen in genetics prenatally ($p<0.001$), and whether genetic testing was recommended by a genetics specialist ($p=0.007$). No statistically significant relationship was found between the remaining factors and whether the case received genetic testing. Results are summarized in Table 17.

Table 17. Comparison of fetal/infant and gestational parent demographic characteristics between perinatal demise subjects who received genetic testing and those who did not.

Factor	Received Genetic Testing					
Fetal/ Infant Demographics	**N**	**Yes n (%)**	**No n (%)**	**$\chi 2$**	**df**	**p-value**
Demise type	111			1.077	1	0.299
SAB-IUFD		33 (50.0%)	33 (40.0%)			
Neonatal death		27 (60.0%)	18 (40.0%)			
Sex	108			1.077	1	0.301
Male		29 (50.9%)	28 (49.1%)			
Female		31 (60.8%)	20 (39.2%)			
Gestational age	111			16.261	1	<0.001
2nd trimester		23 (37.1%)	39 (62.9%)			
3rd trimester		37 (75.5%)	12 (24.5%)			
Ultrasound anomalies	76			16.527	2	<0.001
None detected		9 (39.1%)	14 (60.9%)			
Single system		16 (72.7%)	9 (27.3%)			
Multiple systems		28 (90.3%)	3 (9.7%)			
Soft marker anomalies only	57			2.604	1	0.164 [a]
Yes		2 (50.0%)	2 (50.0%)			
No		44 (83.0%)	9 (17.0%)			
Autopsy done?	111			19.751	2	<0.001
Yes		31 (83.8%)	6 (16.2%)			
No		29 (40.5%)	45 (59.5%)			
Autopsy anomalies by system	37			18.078	2	<0.001[a]
0		1 (20.0%)	4 (80.0%)			
1-3		5 (83.3%)	1 (16.7%)			
4-5		15 (93.8%)	1 (6.2%)			
>=6		10 (100.0%)	0			

[a] 2-sided Fisher's Exact Test

Table 17 (Continued). Comparison of fetal/infant and gestational parent demographic characteristics between perinatal demise subjects who received genetic testing and those who did not.

Factor	Received Genetic Testing					
Fetal/ Infant Demographics	**N**	**Yes n (%)**	**No n (%)**	**$\chi 2$**	**df**	**p-value**
Genetics specialty involved in dysmorphology exam	47			5.218	1	0.042[a]
Yes		15 (100.0%)	0			
No		23 (71.9%)	9 (28.1%)			
DOB before or during COVID-19 pandemic	111			0.423	1	0.516
Pre-pandemic		34 (51.5%)	32 (48.5%)			
During pandemic		26 (57.8%)	19 (42.2%)			
Gestational Parent Demographics	**N**	**Yes n (%)**	**No n (%)**	**$\chi 2$**	**df**	**p-value**
Race/ ethnicity	110			0.673	2	0.714
White Non-Hispanic		16 (61.5%)	10 (38.5%)			
Hispanic		24 (52.2%)	22 (47.8%)			
Other		20 (52.6%)	18 (47.4%)			
Preferred language	111			2.656	1	0.103
English		52 (57.8%)	38 (42.2%)			
Other		8 (38.1%)	13 (61.9%)			
Median income by ZIP code	111			5.145	3	0.161
$39,061-$64,876		11 (42.3%)	15 (57.7%)			
$64,877-$75,218		13 (46.4%)	15 (53.6%)			
$75,219-$96,737		19 (61.3%)	12 (38.7%)			
$96,738-$156,318		18 (69.2%)	8 (30.8%)			

[a] 2-sided Fisher's Exact Test

Table 17 (Continued). Comparison of fetal/infant and gestational parent demographic characteristics between perinatal demise subjects who received genetic testing and those who did not.

Factor	Received Genetic Testing					
Gestational Parent Demographics	**N**	**Yes n (%)**	**No n (%)**	**$\chi 2$**	**df**	**p-value**
AMA at EDD Yes No	111	 19 (52.8%) 41 (54.7%)	 17 (47.2%) 34 (45.0%)	0.035	1	0.852
Marital status Married Non-married	111	 33 (56.9%) 27 (50.9%)	 25 (43.1%) 26 (49.1%)	0.395	1	0.530
Religion declared Yes No	111	 38 (54.3%) 22 (53.7%)	 32 (45.7%) 19 (46.3%)	0.004	1	0.949
Total pregnancies 1-2 >3	111	 27 (60.0%) 33(50.0%)	 18 (40.0%) 33(50.0%)	1.077	1	0.299
Total living children 0-1 >2	108	 38 (57.6%) 20 (47.6%)	 28 (42.4%) 22 (52.4%)	1.023	1	0.312
Insurance provider Private Government	110	 21 (56.8%) 39 (53.4%	 16 (43.2%) 34 (46.6%)	0.110	1	0.740
Insurance provider type PPO Medicaid	89	 18 (64.2%) 31 (50.8%)	 10 (35.7%) 30 (49.2%)	1.406	1	0.236
Seen in genetics prenatally Yes No	111	 29 (78.3%) 31 (41.9%)	 8 (21.6%) 43 (58.1%)	13.222	1	<0.001

Table 17 (Continued). Comparison of fetal/infant and gestational parent demographic characteristics between perinatal demise subjects who received genetic testing and those who did not.

Factor	Received Genetic Testing					
Gestational Parent Demographics	**N**	**Yes n (%)**	**No n (%)**	**$\chi 2$**	**df**	**p-value**
Genetics specialist recommended testing	65			7.245	1	0.007
Yes		27 (96.4%)	1 (3.6%)			
No		26 (70.3%)	11 (29.7%)			

3.2.4 Univariate analysis of factors that may predict abnormal results from genetic testing

Perinatal and gestational parent factors, as outlined in sections 3.1.1, 3.1.2, and 3.1.3, were compared with the reception of abnormal results from prenatal and postnatal genetic testing. An abnormal result was defined as the case receiving a diagnostic testing result or a variant of uncertain significance. Significant relationships were found between the perinatal demise case receiving abnormal genetic testing results and the number of anomalous systems detected on the first anatomy ultrasound (p=0.016), whether a medical geneticist performed a dysmorphology exam (p=0.028), and whether the genetics specialty was involved in the recommendation of genetic testing. Whether the gestational parent was of advanced maternal age at delivery was also associated with an abnormal result from prenatal and postnatal genetic testing (p=0.046). However, when chromosomal conditions were removed from this comparison, there was no longer a significant difference (N=50; $\chi 2$ = 0.965; p = 0.496 by Fisher's exact test). No statistically significant relationship was found

between the remaining factors and whether the case received an abnormal result from genetic testing. Results are summarized in Table 18.

Table 18. Comparison of fetal/infant and gestational parent demographic characteristics between perinatal demise subjects who received abnormal genetic testing results and those who did not.

Factor	Received Abnormal Result					
Fetal/ Infant Demographics	**N**	**Yes n (%)**	**No n (%)**	**$\chi 2$**	**df**	**p-value**
Demise type	60			2.347	1	0.114
SAB-IUFD		13 (39.3%)	20 (60.6%)			
Neonatal death		16 (55.6%)	11 (44.4%)			
Sex	60			0.276	1	0.599
Male		13 (44.8%)	16 (55.1%)			
Female		16 (51.6%)	15 (48.4%)			
Gestational age				1.265	1	0.261
2nd trimester	60	9 (39.1%)	14 (60.9%)			
3rd trimester		20 (54.1%)	17 (45.9%)			
Ultrasound anomalies	53			7.964	1	0.016[a]
None detected		1 (11.1%)	8 (88.9%)			
Single system		7 (43.8%)	9 (56.3%)			
Multiple systems		18 (64.3%)	10 (35.7%)			
Soft marker anomalies only	46			.036	1	1.000 [a]
Yes		1 (50.0%)	1 (50.0%)			
No		25 (56.8%)	19 (43.2%)			
Autopsy anomalies	31			3.139	3	0.371[a]
0		0	1(100.0%)			
1-3		2 (40.0%)	3 (60.0%)			
4-5		9 (60.0%)	6 (40.0%)			
>=6		3 (30.0%)	7 (70.0%)			
Genetics specialty involved in dysmorphology exam	38			3.702	1	0.054
Yes		10 (66.7%)	5 (33.3%)			
No		8 (34.8%%)	15 (65.2%)			

Table 18 (Continued). Comparison of fetal/infant and gestational parent demographic characteristics between perinatal demise subjects who received abnormal genetic testing results and those who did not.

Factor	Received Abnormal Result					
Fetal/ Infant Demographics	**N**	**Yes n (%)**	**No n (%)**	**χ2**	**df**	**p-value**
DOB before or during COVID-19 pandemic?	60			0.051	1	0.798
Pre-pandemic		16 (47.1%)	18 (52.9%)			
During pandemic		13 (50.0%)	13 (50.0%)			
Gestational Parent Demographics	**N**	**Yes n (%)**	**No n (%)**	**χ2**	**df**	**p-value**
Race/ ethnicity	60			0.551	2	0.759
White Non-Hispanic		7 (43.8%)	9 (56.3%)			
Hispanic		12 (50.0%)	12 (50.0%)			
Other		9 (45.0%)	11 (55.0%)			
Preferred language	60			0.434	1	0.510[a]
English		26 (50.0%)	26 (50.0%)			
Other		3 (37.5%)	5 (62.5%)			
Median income by ZIP code	60			3.952	3	0.267
$39,061-$64,876		5 (45.5%)	6 (54.5%)			
$64,877-$75,218		9 (69.2%)	4 (30.8%)			
$75,219-$96,737		6 (33.3%)	12 (66.7%)			
$96,738-$156,318		8 (50.0%)	10 (50.0%)			
AMA at EDD	60			4.493	1	0.034
Yes		13 (68.4%)	6 (31.6%)			
No		15 (35.7%)	27 (64.3%)			
Marital status	60			1.133	1	0.287
Married		18 (54.5%)	15 (45.5%)			
Non-married		11 (40.7%)	16 (59.3%)			

Table 18 (Continued). Comparison of fetal/infant and gestational parent demographic characteristics between perinatal demise subjects who received abnormal genetic testing results and those who did not.

Factor	Received Abnormal Result					
Gestational Parent Demographics	**N**	**Yes n (%)**	**No n (%)**	**$\chi 2$**	**df**	**p-value**
Religion declared	60			0.115	1	0.734
Yes		19 (50.0%)	19 (50.0%)			
No		10 (45.5%)	12 (54.5%)			
Total pregnancies	60			0.244	1	0.622
1-2		11 (40.7%)	16 (59.3%)			
>3		18 (47.1%)	15 (52.9%)			
Total living children	58			1.680	1	0.195
0-1		16 (42,1%)	22 (57.9%)			
>2		12 (60.0%)	8 (40.0%)			
Insurance provider	60			0.212	1	0.645
Private		11 (52.3%)	10 (47.6%)			
Government		18 (46.2%)	21 (53.8%)			
Seen in genetics prenatally	60			2.379	1	0.123
Yes		17 (58.6%)	12 (41.4%)			
No		12 (37.5%)	20 (62.5%)			
Genetics specialty involved in recommending testing	53			13.784	1	<0.001
Yes		20 (74.1%)	7 (25.9%)			
No		6 (23.1%)	20 (76.9%)			

3.2.5 Univariate analysis of factors of genetic testing return and post-test counseling

Of the 60 perinatal demises that received genetic testing pre- and postnatally, the results return to the gestational parent was documented in 37 cases. In 35 cases, the specialist of the returning provider was documented, with the remaining two cases having results returned by a non-UCI provider with post-test counseling records not available for review. Clinic notes were scored on a 6-point scale of patient education points adapted from Baker *et al.*, 2002 & Uhlmann, 2009's patient letter outline to evaluate the quality of documentation of the genetic testing results return (Table 3).

The number of education points was categorized according to whether 1 to 2, 3 to 4, or 5 to 6 education points were discussed to test an association of whether genetics and non-genetics specialists providing the results return documented a statistically significantly different number of patient education points in clinical documentation. A statistically significant difference was found between the number of patient education points provided by genetics versus non-genetics healthcare providers ($p<0.001$) (Table 19).

Furthermore, there was a statistically significant difference between the rate of the number of results returned for abnormal results versus normal genetic testing results, with abnormal results more likely to be returned to the gestational parent. ($p=0.029$) (Table 20). Notably, 7 abnormal results did not have documentation available for results return. In 4 cases, the lead researcher did not find documentation of successful results returns in the databases reviewed. In 2 cases, testing that yielded abnormal results was provided externally, so no documentation of results disclosure was provided. In one case, the gestational parent was late for her post-partum follow-up and left before being seen in

clinic. She declined further follow-up in favor of making an appointment with her obstetrician. Documentation ends following this note.

Table 19. Comparison of the number of post-test patient education topics documented whether a genetics specialist was involved in the genetic testing results return.

	Was a Genetics Specialist Involved in Genetic Testing Results Return?					
Post-Test Result Topics Documented	**N**	**Yes n (%)**	**No n (%)**	**$\chi 2$**	**df**	**p-value**
1-2 3-4 5-6	35	3 (17.6%) 3 (50.0%) 11 (91.7%)	14 (82.4%) 3 (50.0%) 1 (8.3%)	15.435	2	<0.001[a]

[a] 2-sided Fisher's Exact Test

Table 20. Comparison of genetic testing result type and whether genetic testing results were returned to the gestational parent.

Factor	Genetic Testing Results Returned					
Result Type	**N**	**Yes n (%)**	**No n (%)**	**$\chi 2$**	**df**	**p-value**
Normal Abnormal	60	15 (48.4%) 22 (75.9%)	16 (51.6%) 7 (24.1%)	4.785	1	0.029

IV. DISCUSSION

The plateauing rate of the previously declining perinatal death, defined by the summation of fetal and neonatal deaths, is an ongoing challenge in public health. Undiagnosed genetic conditions with potential lethality, including chromosomal disorders and monogenic conditions, are thought to comprise a significant number of perinatal deaths with and without major congenital anomalies. In the case of an undiagnosed medical condition, medical geneticists and genetic counselors are trained to identify possible genetic etiologies through dysmorphology physical examination, personal health history, and a patient's multigenerational family history to suggest appropriate genetic testing that can lead to a possible diagnosis. However, little is known regarding the genetics specialists' contributions to the postmortem healthcare process compared to other healthcare providers in the perinatal space preceding and following a fetal or neonatal death. This study sought to define the utilization of genetics and autopsy services in the case of perinatal demise, comparing the association of gestational parent and perinatal factors on the uptake and results of genetic consult, genetic testing, and diagnostic autopsy. Furthermore, this study aimed to detail the impact genetics versus non-genetics healthcare professionals have on decision-making in genetic testing recommendations, diagnostic yield following genetic testing, post-test counseling, and patient education of post-test genetics results. A retrospective chart review was undertaken for 111 perinatal demise cases occurring at UCI Health from November 1st, 2017, to December 1st, 2021. Perinatal demise cases were studied for gestational parent and perinate demographics associated with attendance of prenatal and postnatal genetics appointments and consults, uptake of

an invasive autopsy, uptake of genetic testing, and diagnostic yield of genetic testing results.

4.1 Attendance of post-delivery genetics consult

This study investigated the impact of gestational parent factors on the attendance of post-delivery genetics consult. Among the demographics evaluated, gestational parents with English listed as their preferred language were more likely to have received a genetics consult ($p=0.021$). In contrast, none of the 21 gestational parents who preferred another language to English received post-delivery genetics consult for their neonate or fetus following delivery or death. The literature documents a precedent of under-referring medically underserved populations to genetics services. A study assessing barriers to referrals to genetics services for hereditary cancer syndromes in the Kaiser Permanente Northwest (KPNW) system found that patients receiving referrals to cancer genetics disproportionately identified as Non-Hispanic White ($p=0.0126$) and primarily English-speaking ($p<0.0001$) when compared to the larger population of KPNW members (Muessig *et al.*, 2022). These findings merit further study regarding potential barriers for non-English speaking patients in accessing post-delivery genetics consult services.

Regarding comparisons of perinatal demographics with the attendance of post-delivery genetics consult, neonatal deaths were more likely to receive consult than intrauterine fetal deaths ($p<0.001$). This comparison suggests that neonates' increased duration of hospital stay increased the chance of receiving a genetics consult compared to fetal deaths. This finding also mirrored the increased likelihood that deliveries occurring in the third trimester of pregnancy were more likely to receive post-delivery genetics consult than those delivered in the second trimester of pregnancy ($p<0.001$). Furthermore, an

increasing number of anomalous body systems detected on the first anatomy ultrasound was also associated with higher attendance rates of post-delivery genetics consults. Indeed, neonates with at least one congenital anomaly have been shown in one study to have a 93% (67/72) rate of confirmed genetic diagnosis, with neonates with multiple congenital anomalies comprising two-thirds of the total with a confirmed genetic diagnosis (Marouane *et al.,* 2022). It follows that perinates in this study with anomalies in one or more than one body system detected on ultrasound would be referred at increasing rates for genetic evaluation given this association.

4.2. Rate of prenatal and postnatal genetic testing reception

The comparison analyses included all genetic testing received prenatally and postnatally by perinatal death cases. In comparing gestational age at delivery of the perinatal death case to the reception of genetic testing, significantly more cases delivered during the third trimester of pregnancy received genetic testing than second-trimester deliveries ($p<0.001$). Most likely, pregnancies maintained through the third trimester had more opportunities to receive prenatal genetic testing.

Postnatally, significantly more perinatal cases received a dysmorphology exam by a medical geneticist in the presence or absence of additional professionals providing a dysmorphology exam, including pathologists, obstetricians, and neonatologists also received genetic testing ($p=0.042$). It should be noted that genetic testing in the case of perinatal demise may not always be indicated, especially if a non-genetic explanation has been established for congenital anomalies. However, these findings suggest that the physical exam by a medical geneticist may promote uptake of genetic testing by the appreciation of subtle dysmorphic features that can expand the differential diagnosis and

recommendations for genetic testing. Indeed, a complete dysmorphology exam by a trained dysmorphologist/ medical geneticist is recommended to discern if subtle dysmorphic features suggest a recognizable genetic syndrome or a familial trait (Solomon & Muenke, 2012). Furthermore, as uptake of broad next-generation sequencing in the form of multigene panel testing, exome sequencing, and even genome sequencing becomes common practice, the dysmorphology exam has an established role in interpreting whether a patient's genotypic findings via genetic testing are consistent with an established disease phenotype (Hurst & Robin, 2020).

In the examination of perinatal demise cases that received genetic testing, cases in which the gestational parent had an estimated median income by ZIP code through the United States Census Bureau's 2016-2020 American Community Survey above the median income of the sample ($75,219) were more likely to receive genetic testing than those cases in which the gestational parent had an estimated income below the median of the sample ($p=0.048$). However, no significant difference was found when the same comparison was made using estimated income quartiles ($p= 0.161$). This finding suggests that income may have played a factor in access to genetic testing. However, comparisons of the insurance provider (private versus government insurance and PPO versus Medicaid) yielded no significant difference in whether genetic testing was received. This study may have had insufficient power to determine differences between insurance provider groups and genetic testing received. Furthermore, estimated income by ZIP code may be an inaccurate estimation of socioeconomic status.

4.3 Autopsy rate

This study gleaned several surprising findings regarding gestational parent and fetal demographics seeking to predict acceptance of autopsy for a perinatal death investigation. The overall perinatal autopsy rate for this study was 38.1%, with 37 perinatal death cases receiving autopsy out of a total of 97 with documented consent offered. This finding closely matched the perinatal autopsy rate of 38% determined by UK national data and higher than in a US study evaluation perinatal death investigation, which found that 30% of perinates received autopsy (Lewis *et al.*, 2018) (Nestander *et al.*, 2021). However, both studies defined perinatal death more narrowly than this study. The UK national data characterized perinatal death as a death occurring from 24 weeks' gestation up to six complete days of life; the US study defined perinatal death as deaths greater than 20 weeks' gestation up to the seventh day of life. When divided by demise type, 14 (21.1%) SAB-IUFDs and 23 (51.1%) neonatal deaths received autopsy in this cohort.

The higher number of neonatal death autopsies in this study than in the literature may suggest differing motivations for autopsy in the study population. Autopsies were performed on significantly more neonatal deaths than SAB-IUFDs (p=0.001). However, there was no significant difference between gestational age at delivery for autopsy uptake (p=0.137). This finding suggests whether the perinate was born living impacted autopsy uptake more than gestational age at delivery. However, this study only considered invasive post-mortem evaluation. Future studies could evaluate if differences in uptake of less invasive post-mortem imaging, including magnetic resonance imaging (MRI), ultrasound, and skeletal survey, impact the autopsy rate between stillbirths and neonatal deaths.

Previous studies have shown that gestational parent factors such as race, ethnicity, and religious affiliation impact autopsy rate uptake (Sauvegrain *et al.*, 2019) (Oliver *et al.*, 2020). Gestational parents of Hispanic descent have been found to have lower rates of fetal autopsy uptake than non-Hispanic black and non-Hispanic white gestational parents (Oliver *et al.*, 2020). However, this study found no statistically significant difference between declared race and ethnicity on autopsy uptake at UCIMC. Possibly, the sample size of this study limited the ability to determine the effect of race and ethnicity on autopsy acceptance. Similarly, no significant difference between religious affiliation and autopsy uptake was found, including no distinction between whether the gestational parent declared a religion or by specific religious affiliation (p=0.493). This study comprised mainly Catholic and non-Catholic Christian gestational parents (61.2%). Non-orthodox Christian religions primarily do not have prohibitions on the practice of fetal autopsy. There was possibly not a large enough representation of gestational parents belonging to faiths that traditionally avoid autopsies, such as Orthodox Judaism and Islam, to observe a perceivable difference (Anderson, 2009).

The results of this study offer an opportunity for review of the autopsy consenting process in view of the relatively low uptake of perinatal autopsy in this cohort (38.1%, N=37/97 of consented cases). Autopsy authorization documentation available through the UCI EMR was reviewed for content (Appendix F). The document discusses in detail the reasons a case may be eligible to receive an autopsy. However, there was limited language describing the handling of specimens and the condition the body or products of conception would be returned to the family (e.g., for burial), if desired: "[The purpose of this autopsy] includes direct examination, photographs, removal, and preservation of any organ or

structure for microscope or other study." The form included areas for the family or consenting provider to write in restrictions or conditions of autopsy authorization. No documentation regarding UCI standard procedure for autopsy consenting was available for review.

Additional study of the verbal consenting process and direct interviews with parents who have undergone the autopsy consenting process could elucidate motivations for accepting or declining perinatal autopsy. A qualitative study by Meaney *et al.* (2015) found that parents' reasons to accept or decline perinatal autopsies are multifactorial, hinging on their understanding of the procedure (which may be largely influenced by depictions of autopsies in popular media or other personal experiences), their grieving emotional state (which may include shock and disbelief regarding the recent demise or pregnancy loss), and a desire to find meaning in the loss. Prior research has also found that parents are more likely to grant permission for an autopsy when consented by a senior member of the medical team (Stock *et al.*, 2010). Additional studies have suggested that having a dedicated team of healthcare professionals trained in autopsy consenting and grief support helped improve autopsy uptake outcomes (Downe *et al.*, 2012; McCreight, 2008). The literature has also emphasized the importance of measures UCI currently takes to reinforce the importance of perinatal autopsy, including regular clinicopathological case conferences that include autopsy findings, to impact autopsy consenting outcomes (Lugli *et al.*, 1999). Evaluation of current practices could establish areas for improvement in conveying the benefits of a perinatal autopsy while taking into account the parents' unique psychosocial situation and state of grief following a perinatal demise or pregnancy loss.

4.4 Impact of genetics involvement on potential diagnostic yield

Another primary aim of this study was to determine factors of genetics specialty participation in a perinatal demise case prenatally and postnatally that contributed to diagnostic yield. In this study, those factors were compared to the numbers of perinatal demise cases that received uninformative results (e.g., negative results) to those that received abnormal, potentially informative results (confirmed diagnostic or uncertain results). For reference, 28 of the 60 cases that underwent genetic testing received an abnormal result, with 24 of those cases receiving diagnostic results and 4 receiving uncertain results. This comparison generated an overall diagnostic yield of 40% and a potential diagnostic yield of 47%.

In investigating gestational parent factors associated with a perinatal demise case receiving an abnormal result, cases in which the gestational parent was of advanced maternal age (35 years or older on the estimated date of delivery) were significantly more likely to receive an abnormal result ($p=0.034$). This finding may be explained by the fact that the risk of a pregnancy having a chromosomal abnormality increases with the age of the gestational parent (Gardner & Sutherland, 2018). Indeed, when abnormal results with chromosomal abnormalities, including aneuploidies and the single case of triploidy, were removed from the comparison, there was no significant difference between whether the gestational parent was of advanced maternal age and whether their pregnancy received an abnormal genetic testing result ($p=0.496$). Thus, these findings are consistent with prior studies into the relationship between maternal age and chromosomal conditions in pregnancy (Gardner & Sutherland, 2018). Additionally, this study found that gestational

parents of advanced maternal age were not more likely to receive prenatal genetic counseling than gestational parents under 35 at the estimated date of delivery., suggesting that the abnormal results of AMA gestational parents were not driven by a disproportionate degree of referrals to prenatal genetics. Although investigations of the effect of paternal age on the incidence of congenital anomalies and genetic conditions have been documented, the ages of sperm donors (i.e., father of the pregnancy) of the pregnancies studied were not available (Janeczko *et al.*, 2020). Future studies could investigate this cohort in the presence of paternal ages to further corroborate these findings in the literature.

This study's findings were unsurprising regarding comparisons of ultrasound findings and diagnostic yield. Cases with anomalies affecting multiple systems were more likely to receive an abnormal testing result than cases that had anomalies affecting a single system or no congenital anomalies detected on ultrasound (p=0.016). Prior research has found that in a fetal cohort of 2086 fetuses, chromosomal anomalies were more often diagnosed by karyotype in fetuses with multisystem malformations (29%) compared to those with isolated defects (2%) (Nicolaides *et al.*, 1992). This suggests that detections of anomalies in multiple body systems are more likely to have a syndromic or genetic etiology than those with isolated malformations. Furthermore, whether the perinate had only soft markers versus at least one non-soft marker anomaly detected on ultrasound was not significantly associated with genetic testing results. However, only two of the four cases with only soft markers detected on ultrasound received genetic testing. Given the small sample size of cases that only had soft makers, this study may not have possessed sufficient power to determine a difference between these groups.

This study found that in three cases (a diagnosis of Triple X syndrome with complex heart defects, a diagnosis of 16p11.2 duplication syndrome with renal pelvis dilation, and a diagnosis of 16p11.2 deletion syndrome with a cleft lip and meningocele), the diagnosis was not consistent with the congenital anomalies noted on ultrasound or postmortem examination and was not known to be associated with perinatal death. The genetics specialist involvement in these cases is documented in Appendix B as Case 2 and Case 10 and in Appendix C as Case 6, respectively. In the case with Triple X syndrome, this diagnosis was made prenatally at a non-UCI affiliated site. No records were available regarding the counseling of the genetic finding following demise, and no follow-up genetic evaluation at UCI was performed. In the case with 16p11.2 duplication syndrome diagnosed by CMA, genetic testing was recommended by obstetrics and was returned by a nurse practitioner. Following the results return, the gestational parent was referred to UCI genetics for genetic counseling, but they were never seen in genetics postmortem. Finally, in the case with 16p11.2 deletion syndrome, the pregnancy was seen in prenatal genetics and referred to a post-delivery genetics consult. However, the perinate died before the consult could be made. Obstetrics attempted to reach the family by phone with the postnatal CMA results and to schedule attendance for a postpartum visit. However, they could not reach the gestational parent. These case studies highlight the importance of continued genetics involvement, especially in cases in which a molecular diagnosis may not explain the demise but may have recurrence implications for family members. Furthermore, despite uncovering an abnormal genotype, a genetics professional may have recommended additional genetic testing targeting clinically significant congenital anomalies in each case.

Genetics healthcare professionals' involvement also significantly impacted whether cases received abnormal results via genetic testing. The likelihood of perinatal demise cases receiving a dysmorphology exam from a medical geneticist as opposed to another medical specialty was associated with receiving an abnormal genetic testing result approached statistical significance ($p=0.054$). Though the literature review gleaned no prior studies investigating the relative contribution of a medical geneticist versus other healthcare professionals to the diagnostic yield based on a dysmorphology exam, the impact of the dysmorphology exam in the literature is established. One study showed that a dysmorphology exam as a standalone test, when performed by a medical geneticist to ascertain gross dysmorphic features and a pathologist to perform a histopathology work-up, identified a definitive genetic diagnosis in 31% (28/90) of cases and a suggested 22% (20/90) of cases that underwent fetal autopsy (Aggarwal *et al.*, 2018). In this study, perinatal demise cases that received genetic testing recommendations from either a medical geneticist or genetic counselor compared to other recommending medical specialties were more likely to receive abnormal results ($p<0.001$). Though limited research has investigated the diagnostic yield of genetic testing ordered by genetics professionals versus non-genetics professionals, one study found that 26% of germline genetic testing orders reviewed by genetic counselors at a reference laboratory were corrected to include testing most appropriate to the patient's clinical indication (Miller *et al.*, 2014). Our study findings suggest that genetics specialists are more likely to order genetic testing that leads to a possible or definitive genetic diagnosis. However, these findings could relate to ascertainment bias and the fact that perinatal cases with multiple congenital anomalies or a highly suspected genetic condition are more readily referred to

genetics for evaluation, leading to a higher rate of diagnosis than those cases not referred to genetics. These findings underscore the importance of the combined effort of the medical geneticist and pathologist in the investigation of perinatal death when a genetic etiology is suspected.

4.5 *Impact of genetics specialty on results return and post-test counseling documentation*

This study provided vital insight into the rate of genetic testing results returns in this postmortem cohort. Of the 31 cases that received entirely negative results, results were returned in 15 (48.4%) cases. Cases that received abnormal results were significantly more likely to have results returned, with 75.9% (22/29) abnormal results returned ($p=0.029$). In 7 cases, no results return was available for review. Of the 7 cases, 1 had testing ordered externally with no follow-up documentation available. One result had attempts made by phone to reach the patient. Furthermore, genetics healthcare professionals were significantly more likely to return abnormal results ($p=0.009$). These findings suggest that genetics specialty involvement positively impacts the rate of results returns. The benefit of returning diagnostic results is clear, with the possibility to discuss how the molecular diagnosis aligns with clinical anomalies and explains the fetal demise, providing closure to the family. Furthermore, post-test genetic counseling can educate the parents regarding recurrence risk for future pregnancies and may inform cascade testing in the family if the genetic variant that was implicated in the demise was inherited, exemplified by the two cases of autosomal recessive polycystic kidney disease and the one cause of Hemoglobin Barts syndrome in this study (Appendix C). Return of normal results, especially in the context of genetic specialty involvement, can provide an opportunity to

explore additional testing that may be indicated following a normal result. Given these benefits, a review of patient follow-up practices may be warranted to close the gap between unreturned abnormal and normal results.

The final aim of this study was to evaluate the degree of post-test counseling documentation provided by genetics versus non-genetics healthcare providers. For the 33 results return cases that received genetic testing, genetics professionals were more likely to document a higher number (5 to 6 points) of post-test counseling topics during the visit to return results detailed in Table 14. However, genetics healthcare professionals were more likely to provide post-test counseling for abnormal results than non-genetics healthcare professionals. Furthermore, cases with abnormal results were more likely to receive more detailed documentation of counseling points discussed. Although factors of genetics involvement, the number of counseling points documented, and whether a genetic testing result was abnormal are highly linked, these results suggest the value of inclusion of genetics healthcare professionals in the genetic testing ordering process from pre-test to post-test counseling. Genetics healthcare professionals are trained to document the result of genetic testing for the understanding of patients and non-genetics providers. This inclusion of detailed documentation that provides a summary of the patient's pertinent prior medical history, family history, and interpretation of results enables continuity of care for individuals with a suspected genetic condition among their multiple healthcare providers, even in the presence of noninformative genetic testing (Hunt Brendish *et al.*, 2021).

In the current study, cases with normal results were more likely to receive a lower number of counseling points documented (1-2 points). This translated to the provider documenting at most that the negative results were discussed with the patient, and a review of fetal anomalies was performed. However, discussions of recurrence risk based on negative results also are necessary to document to convey complete counseling. Importantly, providers must be able to communicate that accurate calculations of recurrence risk in the occurrence of miscarriage with or without fetal anomalies cannot be provided in the presence of a negative result. Negative results themselves do not rule out a possible genetic cause for disease and may indicate more comprehensive genetic testing. These findings suggest a need to standardize results return information when non-genetics professionals provide genetic counseling and for substantial involvement of healthcare professionals with genetics-related training to be involved in the genetics evaluation process from pre-test to post-test counseling. Additionally, further study could investigate whether modality of the results return, including whether results were returned over the phone, via a scheduled telehealth visit, or in an in-person post-partum visit, alters the likelihood that a gestational parent will receive a referral to genetics and attend the visit following results return. Lack of attendance to genetics referrals made by non-genetics professionals following a genetic testing results return may translate to missed opportunities for a genetic professional's continued diagnostic appraisal and recommendations for the family.

4.6 Impact of COVID-19 pandemic on perinatal demise investigation

The study period for this retrospective chart review provided unique insight into the effects of the onset of the COVID-19 pandemic on perinatal death investigation. The COVID-19 pandemic declared by the World Health Organization on March 11, 2020, has had unprecedented impacts on the US health system. However, little research has been done to investigate the impact of the COVID-19 pandemic on the rate of autopsy and genetic services, let alone in cases of perinatal death cause investigation. This study provided a distinct opportunity to study comparisons between perinatal death cases with the age of delivery pre- and post-onset of the COVID-19 pandemic and whether an autopsy was performed, whether genetic testing was received pre- or postnatally, and whether a post-delivery genetics consult was received. All three comparisons proved not to be statistically significant. These results potentially highlight that autopsy and genetic services were maintained as essential encounters during the onset of the COVID-19 pandemic. Although this study did not evaluate the use of different service delivery models, consult services that did not require direct patient contact, such as administration of testing recommendations or genetic counseling sessions, could have been completed by contactless methods such as video or phone visits. Implementation of flexible telehealth models may have enabled continuity of care during the onset of the pandemic. Preliminary research reveals that patients scheduled and seen in a prenatal genetic counseling clinic did not differ significantly from pre-pandemic levels following a transition to a majority telehealth consultation model (Mann *et al.*, 2021). More research is needed to determine the effects on autopsy uptake and attendance of NICU genetics consults. However, these

data tentatively suggest that pandemic-era operations did not significantly affect outcomes of perinatal death investigation based on metrics evaluated.

4.7 Study limitations and future research directions

Although this study's findings largely align with prior research for diagnostic test yield and investigations in genetics involvement, there are several limitations to the study design for which to account. The most significant limitation of this study was the ascertainment of internal and external documents through the UCIMC electronic medical record. The data collection method through the UCI electronic medical record limited the ability to determine if records that were not available for review in the EMR indicated that procedures were not done or if existing documentation was available through an external provider that was not part of UCIMC. As a result, there may have been limited power to discern differences between groups, especially in comparisons that included variables limited by documentation such as ultrasound findings.

Additionally, this study design did not account for the chronology of when cases received the first anatomy ultrasound, prenatal genetic counseling, post-delivery genetics consult, autopsy, and genetic testing. Further research could extend this study to include how the timing of service reception affects the yield and timeliness of diagnostic outcomes for families. Furthermore, the primary focus of this study was on diagnostic genetic testing results. Further studies could include prenatal screening results that initially bring eventual perinatal demise cases to attention, including positive maternal serum and cell-free DNA screening for aneuploidies, neural tube defects, abdominal wall defects, congenital anomalies, and early demise. Beginning in September 2022, the state of

California will transition its statewide prenatal screening program to replace the current options of integrated sequential, serum integrated, and quad marker with cell-free DNA (cfDNA) and maternal serum alpha-fetoprotein only. This program change will enable more gestational parents to access more accurate population-based screenings for trisomy 21, trisomy 18, and trisomy 13 (*California Prenatal Screening Program Changes,* 2022). This contrasts the previous system of *ad hoc* offerings of cfDNA screening to gestational parents based on specific indications, including advanced maternal age, abnormal ultrasound findings, or positive results on maternal serum screening. Such changes will provide new opportunities to ascertain potential perinatal deaths and pregnancy losses based on the more widespread implementation of cfDNA screening.

Regarding the evaluation of documentation of post-test genetic counseling, this study aimed to document the volume of documentation made by genetics versus non-genetics healthcare professionals following a post-test counseling encounter. Future studies could determine which points of counseling genetics versus non-genetics professionals were more likely to cover based on the type of result given (negative, VUS, or positive).

Finally, this study embarked on a primarily univariate analysis of genetic specialty involvement factors associated with outcomes in perinatal death cases. However, factors of genetics involvement, such as attendance to genetics consult, dysmorphology exam, and test recommendation, carry the possibility of an overlapping effect on diagnostic outcomes. An extension of this study could generate models using multivariate analysis to identify predictors of outcomes of genetics evaluation.

4.8 Conclusion

In conclusion, this study found that of the 111 perinatal deaths (the summation of fetal deaths greater than or equal to 20 weeks' gestation and neonatal deaths less than or equal to 28 days of life) studied, 17% (N=19) received post-delivery genetics consult, 33% (N= 37) received autopsy, and 54% (N=60) received at least one form of genetic testing pre- or postnatally. 40% of those that received genetic testing (N=24) received a positive result. Perinatal factors including demise type, gestational age at delivery, and increasing ultrasound anomalies were associated with higher attendance rates of post-delivery genetics consult by a medical geneticist. Genetics involvement factors, including whether the perinate had been evaluated prenatally in a prenatal genetic clinic, a medical geneticist had performed a dysmorphology exam post-delivery, or a genetics healthcare professional had recommended genetic testing, were all significantly associated with an increased likelihood of receiving genetic testing pre- or postnatally. This study found limited gestational parent factors associated with post-delivery genetics consult attendance, autopsy uptake, and reception of pre- and postnatal genetic testing. Gestational parents with English as a preferred language were more likely to have their perinate seen for post-delivery genetics consult than gestational parents with a non-English preferred language. However, religious affiliation, race and ethnicity, median family income by ZIP code, and insurance type of gestational parents were not significantly associated with uptake of autopsy or genetics services during and following pregnancy ending in perinatal demise. Neonatal deaths were significantly more likely to receive autopsy than SAB-IUFDs. Further studies investigating perinatal demise in conjunction with genetics services may benefit from a larger sample size to establish sufficient power to determine differences between

groups. Despite those study limitations, these findings reinforce the importance of genetics healthcare professionals in an interdisciplinary perinatal care setting and in the case of perinatal demise.

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Appendix A:
Letter of approval through
UCI IRB expedited review: Category 5

UCI University of California, Irvine

December 1, 2021

Etta D'Orazio
Genetics

RE: UCI IRB #211 Evaluating uptake and impact of genetic and genomic evaluation following perinatal demise

The above-referenced human-subjects research project has been approved by the University of California, Irvine Institutional Review Board (UCI IRB). This approval is limited to the activities described in the approved protocol and extends to the performance of these activities at each respective site identified. In accordance with this approval, the specific conditions for the conduct of this research are listed below, and informed consent from subjects must be obtained unless otherwise indicated below. Additional conditions for the general conduct of human-subjects research are detailed on the attached sheet.

NOTE: Approval by the Institutional Review Board does not, in and of itself, constitute approval for the implementation of this research. Other institutional clearances and approvals may be required. Research undertaken in conjunction with outside entities, such as drug or device companies, are typically contractual in nature and require an agreement between the University and the entity. Such agreements must be executed by an institutional official in Sponsored Projects, a division in the UCI Office of Research. The University is not obligated to legally defend or indemnify an employee who individually enters into these agreements and investigators are personally liable for contracts they sign. **Accordingly, the project should not begin until all required approvals have been obtained.**

Questions concerning the approval of this research project may be directed to the Office of Research, 160 Aldrich Hall, Irvine, CA 92697-7600; 949-824-6068, 949-824-2125, or 949-824-0665 (biomedical committee) or 949-824-6662 (social-behavioral committee).

Expedited Review: Category 5

Jessica Sheldon, CIP
Alternate Member, Institutional Review Board
Approval Issued: 12/01/2021
Expiration Date: 11/30/2024
UCI (FWA) 00004071, Approved: January 31, 2003

Important Reminder: **UCI is in Research Phase 4 as of June 22, 2021. UCI's research activities will increase over time in parallel with the stages in California's Pandemic Roadmap and other public health and higher education guidance. Refer to the Office of Research webpage on Research Continuity for more details.**

IRB Determinations as Conditions of Approval:
Pregnant Women, Fetuses and Neonates:
1. 45 CFR 46.204(d):[1]

Informed Consent Determinations:
2. Waiver of Informed Consent Granted
3. Waiver of UC HIPAA Research Authorization Granted

[1] *The IRB determined that all of the applicable conditions under Subpart B 45 CFR 46.204(a-j) have been met.* ***Although there is no direct benefit to the mother or fetus, the risk to the fetus is not greater than minimal and the purpose of the research is the development of biomedical knowledge which cannot be obtained by any other means.***

Appendix B. Fetal death cases with a pathogenic finding on genetic testing and congenital anomalies (N=11)

Case No.	Age at Demise (WGA)	Ultrasound Findings	U/S WGA	Result of DM Exam	DM Exam Performed by	Seen in Genetics	Received GT *(Recommended by)*	GT *(returned by)*	Dx	Anomalies C/W Genotype
1	22	Abnormal profile, hypoplastic middle phalanx of fifth digit, ventricular septal defect	18 5/7	None	None	Prenatal GC – Positive maternal serum screen for T21	Prenatally *(External)*	Karyotype – Trisomy 21 *(External)*	Trisomy 21	Yes
2	21	Absent pulmonary valve with mild stenosis and severe regurgitation, moderate dilation right atrium and right ventricle, diminished right ventricle systolic function, moderate tricuspid regurgitation, apical ventricular septal defect, dilation of pulmonary artery, moderate dilation of the ascending aorta	19 2/7	None	None	Prenatally	Prenatally *(External)*	Karyotype – Triple X Syndrome *(External)*	Triple X Syndrome	No

Abbreviations: AMA = Advanced maternal age; C/W = Consistent with; DM = Dysmorphology; Dx = Diagnosis; GC = Genetic counseling; GT = Genetic testing; NIPT = Non-invasive-prenatal testing; SCD = Smith-Lemli-Optiz Syndrome, Congenital Abnormalities, or Fetal Demise; T18 = Trisomy 18; T21 = Trisomy 21; U/S = Ultrasound; VUS = Variant of uncertain significance; WGA = Weeks gestational age

Appendix B (Continued). Fetal death cases with a pathogenic finding on genetic testing and congenital anomalies (N=11)

Case No.	Age at Demise (WGA)	Ultrasound Findings	U/S WGA	Result of DM Exam	DM Exam Performed by	Seen in Genetics	Received GT *(Recom-mended by)*	GT *(returned by)*	Dx	Anomal-ies C/W Genotype
3	26	Ventricular septal defect, omphalocele, dandy walker malformation, absent cerebellar vermis, lemon shaped fetal head	18 6/7	None	None	Prenatal GC-Positive maternal serum screening for T18 and SCD	Prenatally *(Genetics)*	Karyotype -Trisomy 18 *(Genetics)*	Trisomy 18	Yes
4	33	Semilobar holoprosenceph-aly, proboscis, pulmonary atresia/ stenosis, polyhydramnios	26	Proboscis, agnathia, astomia, synotia, hypoplastic upper airway, absence of right olfactory nerve, absence of optic nerve and optic chiasm	Medical Genetics, Pathology (autopsy)	Prenatally; Postmortem Genetics Consult	Prenatally, Following delivery *(Genetics)*	Microarray – normal Panel-OTX2 c.254G>A (P.Trp85*) *(Genetics)*	Syndromic Microphthalmia	Yes

Appendix B (Continued). Fetal death cases with a pathogenic finding on genetic testing and congenital anomalies (N=11)

Case No.	Age at Demise (WGA)	Ultrasound Findings	U/S WGA	Result of DM Exam	DM Exam Performed by	Seen in Genetics	Received GT *(Recommended by)*	GT *(returned by)*	Dx	Anomalies C/W Genotype
5	34	Large bilateral choroid plexus cysts, normal cavum septi pellucidi not seen, possible defect in cerebellar vermis, omphalocele, absent stomach bubble, abnormal cardiac axis, two vessel cord, clenched hands, ambiguous genitalia	17 3/7	small bowel protruding out of the abdomen, cord originating from the bowel site, two vessel cord, Normally formed upper extremities with hyperflexed wrists bilaterally, clenched right thumb, hands bilaterally with 5 fingers each, normally formed lower extremities with 5 toes each. Rocker-bottom foot	Obstetrics	Prenatal GC – Positive NIPT for T18	Following delivery *(Genetics)*	Karyotype – Trisomy 18 *(Obstetrics)*, NIPT results discussed with GC	Trisomy 18	Yes

Appendix B (Continued). Fetal death cases with a pathogenic finding on genetic testing and congenital anomalies (N=11)

Case No.	Age at Demise (WGA)	Ultrasound Findings	U/S WGA	Result of DM Exam	DM Exam Performed by	Seen in Genetics	Received GT *(Recommended by)*	GT *(returned by)*	Dx	Anomalies C/W Genotype
6	31	Two vessel cord, polyhydramnios, marginal cord insertion, abnormal cavum septi pellucidi, possible atrioventricular septal defect	24	None	None	Prenatal GC - AMA	Prenatally *(Genetics)*	Karyotype & FISH – Trisomy 18 *(Genetics)*	Trisomy 18	Yes
7	32	Absent cavum septi pellucidi, fetal echogenic intracardiac focus	17 5/7	Widened and short neck, retrognathia, flattened nasal bridge, mild cardiomegaly, severe hepatomegaly	Pathology (autopsy)	Following Delivery	Prenatally *(Obstetrics)*	Karyotype – Trisomy 21 *(Obstetrics)*	Trisomy 21	Yes
8	27	Nuchal fold 9.1mm, polyhydramnios, absent nasal bone, intracardiac echogenic foci	18 6/7	Low set with small overfolded pinnae and periorbital swelling, extensive loose nuchal skin folds, Widened and flat nasal bridge, ASD	Medical Genetics, Pathology (autopsy)	Prenatal MD Geneticist ; Following Delivery MD Geneticist	Prenatally *(Obstetrics, Genetics)*	Karyotype-Normal Microarray – normal Panel - SOS1 c.2536G>A (p.Glu846Lys) *(Genetics)*	Noonan-Spectrum Disorder	Yes

Appendix B (Continued). Fetal death cases with a pathogenic finding on genetic testing and congenital anomalies (N=11)

Case No.	Age at Demise (WGA)	Ultrasound Findings	U/S WGA	Result of DM Exam	DM Exam Performed by	Seen in Genetics	Received GT *(Recommended by)*	GT *(returned by)*	Dx	Anomalies C/W Genotype
9	23	None	N/A	Overlapping head bones, prominent forehead	Pathology (autopsy)	None	Following Delivery *(Obstetrics)*	Microarray - arr(13)x2-3 *(Obstetrics)*	Trisomy 13, mosaic	Yes
10	23	Renal pelvis dilation	19 3/7	No obvious internal or external anomalies noted	Pathology (autopsy)	None	Following Delivery *(Obstetrics)*	Microarray- 16p11.2 duplication *(Nurse practitioner)*	16p11.2 duplication syndrome	No
11	20	Echogenic focus in the left ventricle, choroid plexus cyst	18 4/7	None	N/A	Prenatally – Positive maternal serum screen for T21 and abnormal U/S findings	Following Delivery *(Obstetrics, Genetics)*	Microarray – Triploidy *(Nurse practitioner)*	Triploidy	Yes

Appendix C. Neonatal death cases with a pathogenic finding on genetic testing and congenital anomalies (N=13)

Case No.	Age at Demise (DOL)	Ultrasound Findings	U/S WGA	DM Exam Findings	DM Exam by	Seen in Genetics	Received GT *(Recommended by)*	GT *(returned by)*	Dx	Anomalies C/W Genotype
1	1	Bilateral echogenic enlarged kidneys, slightly distended stomach	19 4/7	Photographs only - Dysmorphic features related to Potter's sequence	Medical Genetics	Prenatally – abnormal U/S Postnatally	Following Delivery *(Genetics)*	Panel – biallelic mutations in PKHD1 *(Genetics)*	ARPKD	Yes
2	5	No U/S documented	N/A	Cardiogenic non-immune fetal hydrops, fused eyelids, tongue protuberant, bilateral single palmar creases, wide-spaced nipples, ASD	Medical Genetics, Pathology (autopsy)	Postnatally - Suspected hydrops fetalis	Following Delivery *(Genetics)*	Microarray: Xq21.1 duplication VUS; Alpha globin gene panel – negative; Exome: RIT1 c.246T>G (p.Phe82Leu) (pathogenic) *(Genetics)*	Noonan-Spectrum disorder	Yes
3	1	Records not available, mention of "possible cardiac defect"	N/A	Macrosomia, organomegaly, ASD, atypical renal dysplasia	Medical Genetics, Pathology (autopsy)	Postnatally – syndromic diagnosis	Following Delivery *(Genetics, neonatology)*	Microarray: Genome-Wide Uniparental Isodisomy (1-22,X)x2 mos *(Nurse practitioner)*	BWS	Yes

Abbreviations: AMA = Advanced maternal age; ARPKD = Autosomal recessive polycystic kidney disease; ASD = Atrial septal defect; BWS = Beckwith-Wiedemann Syndrome; C/W = consistent with; CSP = Cavum septi pellucidi; DM = Dysmorphology; DOL = Days of life; Dx = Diagnosis; EIF = Echogenic intracardiac focus; GC = Genetic counseling; GT = Genetic testing; NIPT = Non-invasive-prenatal testing; SCD = Smith-Lemli-Optiz Syndrome, Congenital Abnormalities, or Fetal Demise; T18 = Trisomy 18; T21 = Trisomy 21; U/S = Ultrasound; VSD = Ventricular septal defect; VUS = Variant of uncertain significance

Appendix C (Continued). Neonatal death cases with a pathogenic finding on genetic testing and congenital anomalies (N=13)

Case No.	Age at Demise (DOL)	Ultrasound Findings	U/S WGA	DM Exam Findings	DM Exam by	Seen in Genetics	Received GT *(Recommended by)*	GT *(returned by)*	Dx	Anomalies C/W Genotype
4	2	Fetal heart appears large, apparent right ventricular thickening, bowel appears echogenic, upper lift appears flattened, possible hypospadias	20	Non-immune fetal hydrops, severe anasarca, diffuse intra-alveolar hemorrhage with early acute hyaline membrane disease, severe hepatomegaly, marked cardiomegaly	Pathology (autopsy)	Genetics consult by phone Following delivery	Following Delivery *(Neonatology)*	Microarray: 11p15.4 deletion (VUS); Panel: SPTA1 c.5572C>G p.Leu1858Val (VUS); Panel: HBA1/HBA2 alpha globin gene locus : homozygous 20kb --SEA Deletion (Pathogenic) *(Neonatology)*	Hemoglobin Barts syndrome	Yes
5	12	EIF, increased nuchal fold, bilateral pyelectasis	20	Excess nuchal fluid, Lowset, crumpled ears, overfolded upper pinna. Horizontal crease of pinnae noted, hydrops	Medical Genetics	Following Delivery	Following Delivery *(Genetics)*	Microarray: Trisomy 21 *(Not documented)*	Trisomy 21	Yes

Appendix C (Continued). Neonatal death cases with a pathogenic finding on genetic testing and congenital anomalies (N=13)

Case No.	Age at Demise (DOL)	Ultrasound Findings	U/S WGA	DM Exam Findings	DM Exam by	Seen in Genetics	Received GT *(Recommended by)*	GT *(returned by)*	Dx	Anomalies C/W Genotype
6	2	Cleft lip, lumbosacral meningocele with lack of normal develop of the lumbosacral spine	25 3/7	Short webbed necked, Short anteverted nares, wide mouth, broad forehead, diaphragmatic hernia, small phallus, bilateral undescended testes, no buttock definition, off center anal opening, bilateral equinovarus	Medical Genetics, Pathology (autopsy)	Prenatally – fetal anomalies Postnatally – diaphragmatic hernia	Following Delivery *(Genetics)*	Microarray 16p11.2 proximal deletion *(Not documented)*	16p11.2 deletion syndrome	No
7	1	Micrognathia, bilateral club feet, abnormal right arm and hand, possible left hand malformation, dangling choroid plexus without ventriculomegaly, short humerus right arm	19	midface hypoplasia, micrognathia, malformed external ears, frontal bossing, flexion and rotation contractures of the elbows and ankles, absent thumbs, and radioulnar synostosis	Medical Genetics, Pathology (autopsy)	Prenatally – U/S anomalies; Following delivery	Following Delivery *(Neonatology, Genetics)*	Microarray: 1q21.2q21.3 deletion, including SF3B4 gene *(Obstetrics, Genetics)*	Nager syndrome	Yes

Appendix C (Continued). Neonatal death cases with a pathogenic finding on genetic testing and congenital anomalies (N=13)

Case No.	Age at Demise (DOL)	Ultrasound Findings	U/S WGA	DM Exam Findings	DM Exam by	Seen in Genetics	Received GT *(Recommended by)*	GT *(returned by)*	Dx	Anomalies C/W Genotype
8	2	No anomalies detected	19 5/7	bilaterally enlarged kidneys, lowset ears, Potter's sequence anomalies including flattened bridge of the nose, ears flattened against the head, and a calcaneovarus deformation of the right ankle	Medical Genetics, Pathology (autopsy)	Following delivery	Following Delivery *(Genetics)*	Microarray: Normal male Panel: PKHD1 c.4838G>A (p.Cys1613Tyr) (VUS), PKHD1 c.6122G>T (p.Gly2041Val) (Pathogenic) *(Genetics)*	ARPKD	Yes
9	3	Shortened long bones, bell shaped thorax	19 5/7	Large fontanelles, thorax narrow at apex, shortened limbs with severe bowing	Medical Genetics	Prenatally – suspected skeletal dysplasia on U/S; Postnatally	Following Delivery *(Genetics)*	Panel: COL1A1 c. 1353+4dupA *(Genetics)*	OI	Yes

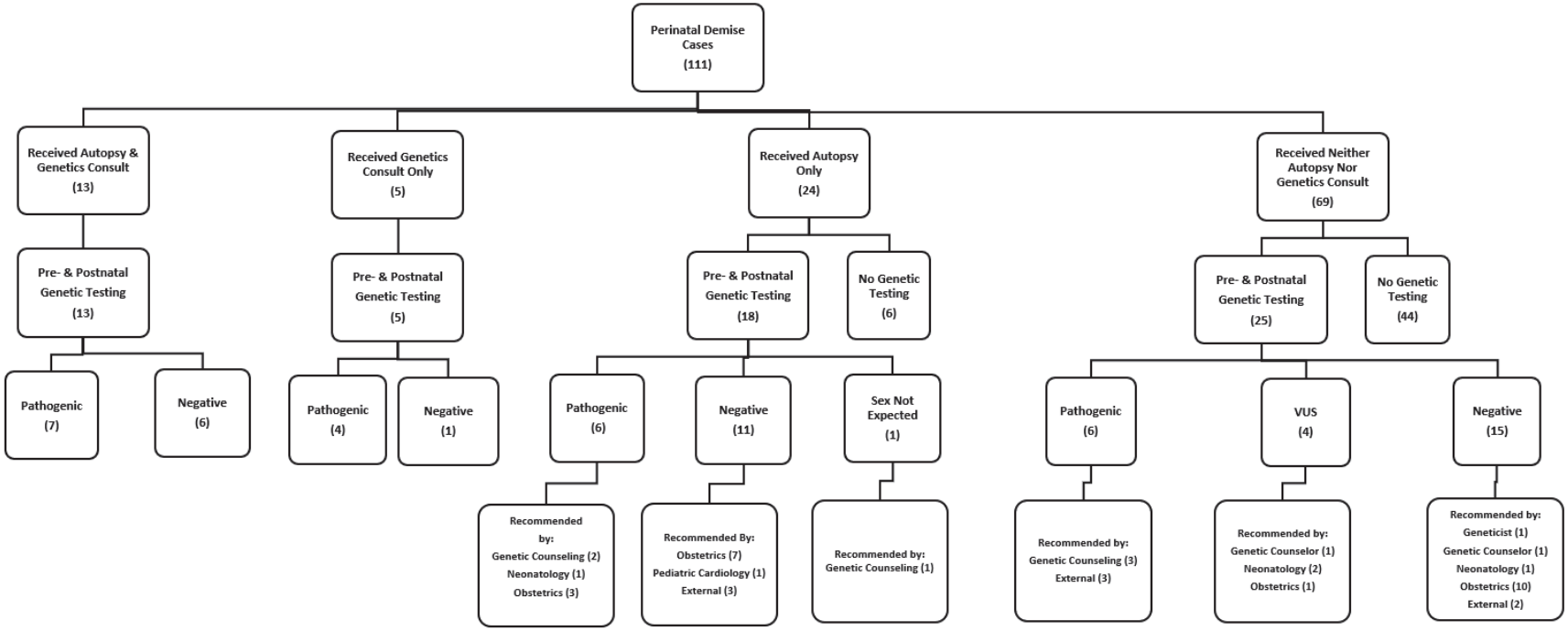
Appendix C (Continued). Neonatal death cases with a pathogenic finding on genetic testing and congenital anomalies (N=13)

Case No.	Age at Demise (DOL)	Ultrasound Findings	U/S WGA	DM Exam Findings	DM Exam by	Seen in Genetics	Received GT *(Recommended by)*	GT *(returned by)*	Dx	Anomalies C/W Genotype
10	1	Micromelia, talipes, possible pulmonary hypoplasia/ bell shaped chest, short ribs, strawberry skull, thanatophoric dysplasia suspected	20 3/7	shortened limbs, curved femurs, flattening of the vertebral bones, and abnormal endo-chondral ossification	Pathology (autopsy)	Prenatally – abnormal U/S	Following Delivery *(Genetics)*	Panel: FGFR3 c.746C>G (p.Ser249Cys) PATH, FGFR3 c.2417C>T (p.Thr806Met) VUS *(Obstetrics, genetics)*	Thanato-phoric Dysplasia	Yes
11	3	Brachycephaly, micromelia, bowing of the long bones, distortion of left femur, small bell-shaped chest, levorotated cardiac axis, flattened nasal bridge	19	Macrocephaly, brachycephaly, small ears, flattened midfacies, anteverted nares, small bell-shaped chest, clavicles and patella not palpated, trident hand, dysplastic finger and toenails	Medical Genetics	Prenatally – Large NT 5.0mm; Following delivery	Following Delivery *(Genetics)*	Panel FGFR3 c.1118A>G, p.Tyr373Cys (pathogenic) *(Not documented)*	Thanato-phoric dysplasia	Yes

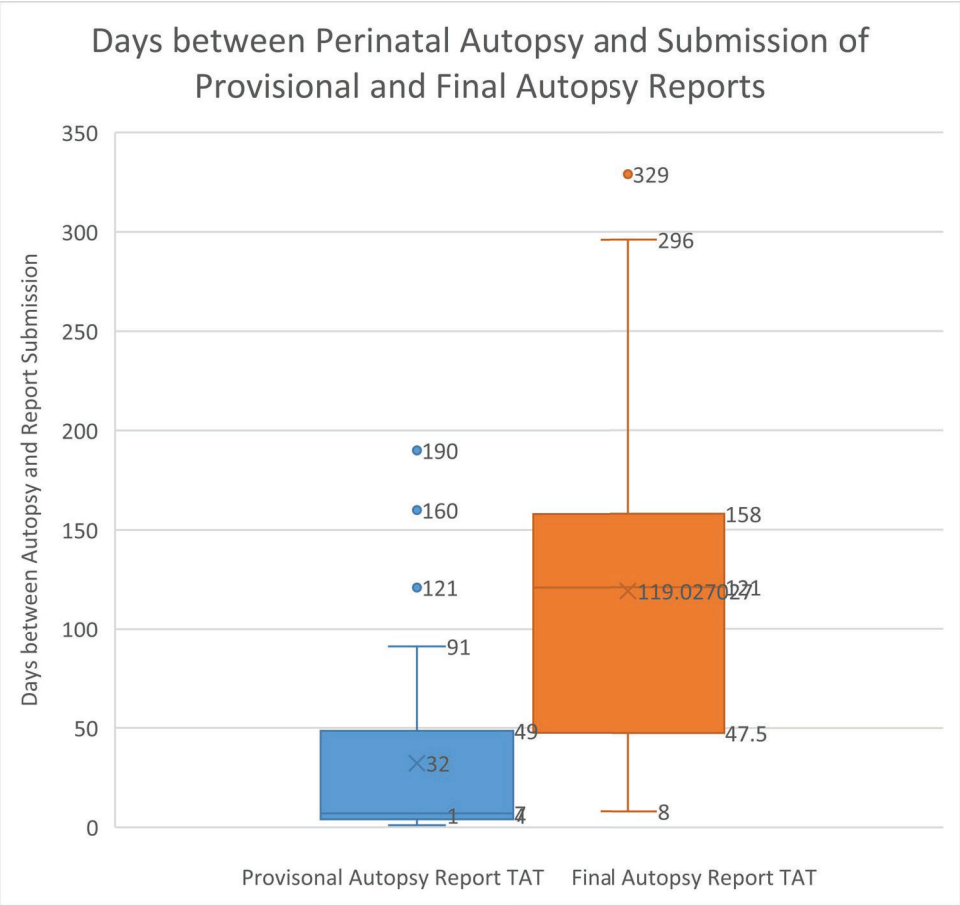
Appendix C (Continued). Neonatal death cases with a pathogenic finding on genetic testing and congenital anomalies (N=13)

Case No.	Age at Demise (DOL)	Ultrasound Findings	U/S WGA	DM Exam Findings	DM Exam by	Seen in Genetics	Received GT *(Recommended by)*	GT *(returned by)*	Dx	Anomalies C/W Genotype
12	3	Femur length is significantly short; Lower limbs appear abnormally short	21 2/7	frontal bossing, macrocephaly, mild micrognathia, small chest and micromelia and features of skeletal dysplasia including a 'butterfly' T5 vertebral body, shortened femurs and humeri, and absence of pubic bones.	Pathology (autopsy)	Prenatally – suspected fetal skeletal dysplasia	Following Delivery *(Genetics)*	Panel: COL2A1 c.1358 G>A p.G453D DDR2 c.1153 A>T (p.Thr-385Ser) *(Genetics)*	COL2A1-related disorder	Yes
13	3	Abnormal CSP, small cerebellum, thickened nuchal fold, VSD, abnormal 3vt view with dilate ductal appearance, abnormal 4 chamber heart, abnormal aortic arch, flat profile, suspected rocker bottom feet	20 1/7	None documented	N/A	Prenatally – fetal anomalies	Prenatally *(External)*	Karyotype – Trisomy 13 *(Genetics)*	Trisomy 13	Yes

Appendix D: Flowchart of perinatal post-delivery and post-mortem services



Appendix E:



Submission attributes for provisional and final autopsy reports were documented. Dates of submission were recorded from the EMR of the gestational parent of SAB-IUFDs or the neonatal death. The mean turnaround time for provisional autopsy reports from the time of autopsy to submission to the EMR was 32.22 days with a median of 7 days, a standard deviation of 46.92 with a range of 1-190 days. The mean turnaround time for final autopsy reports from the time of autopsy to submission to the EMR was 118.14 days, a median of 121 days, and a standard deviation of 78.53 days with a range of 8-329 days. In all 37 cases, preliminary autopsy findings were attempted to be discussed with the ordering physician.

Appendix F:
Authorization for autopsy

Patient Label

UNIVERSITY of CALIFORNIA • IRVINE
HEALTHCARE

AUTHORIZATION FOR AUTOPSY

AUTOPSY CRITERIA

It shall be the duty of all Physicians to attempt to obtain autopsies on all patients who expire at UC Irvine Healthcare. An autopsy may be performed only after obtaining consent as defined by state law. All autopsies shall be performed by a physician assigned responsibility by the Department of Pathology. The Medical Staff will use the criteria listed below to obtain autopsies.

**NOTE: The criteria with double asterisks are within the jurisdiction of the Orange County Coroner. See complete list of the criteria for Coroner's jurisdiction behind the "Report of Death or Stillborn" form: causes of death in that list must be reported by telephone to the Coroner. Deaths waived thereafter by the Coroner, and all other deaths, are to be considered for autopsy. Specific reasons to emphasize the autopsy might include the following criteria:

a. Unexpected or unexplained deaths occuring during or following any dental, medical, or surgical diagnostic procedures and/or therapies.**

b. Deaths of patients who have participated in clinical trials (protocols) approved by institutional review boards. **

c. All obstetric deaths. **

d. Deaths known or suspected to have resulted from environmental or occupational hazards. **

e. Death in which autopsy may help to explain unknown and unanticipated medical complications to the attending physician.

f. All deaths in which the cause of death or a major diagnosis is not known with reasonable certainty on clinical grounds.

g. Causes in which an autopsy may help to allay concerns of, and provide assurance to, the family and/or the public regarding the death.

h. Unexpected or unexplained deaths that are apparently natural and not subject to forensic medical jurisdictions.

i. Natural deaths that are subject to, but not waived by, a forensic medical jurisdiction, such as persons dead on arrival at hospitals, deaths occuring in hospitals within 24 hours of admission, and deaths in which the patient sustained an injury while hospitalized.

j. Deaths resulting from high-risk infections and contagious diseases.

k. All perinatal and pediatric deaths.

l. Deaths in which it is believed that an autopsy would disclose a known or suspected illness that may have a bearing on survivors or recipients of transplant organs.

1. An autopsy is being requested on
Se esta solicitando se haga una autopsia en:

_____
Name of the deceased/Nombre de la persona fallecida

2. For the purpose of: (List the indication or circle the appropriate criterion in the list located to the left)
Con el propósito de: (Indique la razón o coloque un circulo sobre lo que aplique en la lista localizada a la izquierda)

_____

_____

3. This includes direct examination, photographs, removal and preservation of any organ or structure for microscopic or other study.
Esto incluye un examen directo, fotografias, extirpación de cualquier órgano o estructura para estudios microscópcos o de otra naturaleza.

4. Restrictions or conditions of this authorization are: (specify "none" or restrictions desired).
Las restriccíones o condiciones de esta autorización son las siguientes:
(especifique "ninguna" o indique las deseadas)

_____

_____

I give my authorization for the autopsy.
Doy mi autorización para la autopsia.

❑ Yes/Si ❑ No

_____ _____
Signature/Firma Date/Time/Fecha y Hora

_____ _____
Print name **Relationship**

_____
Relationship to deceased (spouse, adult child, parent, adult brother or sister, legal guardian, other person authorized to control disposition).

Indique el parentesco o la relación con la persona fallecida (esposo(a), hijo(a) adultos, padre o madre, hermano(a) adultos, tutor legal, o persona autorizada para tomar este tipo de determinación)

_____ _____
Witness/Testigo Date/Time/Fecha y Hora

_____
Printed name, service, pager of requesting physician
Nombre en letra de molde, servicio, pager del médico solicitante

_____
Attending Physician's Name (if not the requesting physician)
Nombre del médico en jefe y servicio (si es otro fuera del médico solicitante)

_____ _____
Attending Physician's Signature Date/Time/Fecha y Hora

85555

All documentation must indicate the specific date and time of entry and a signature complete with identifying credential, title or classification.

85555 (Rev. 6/28/11)

Original to Pathology, Yellow copy to patient's medical record