

Genetic counseling for advanced paternal age: a survey of genetic counselors' current practice

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## Abstract

Advanced paternal age (APA) has no formal definition, though many publications utilize the cutoff of fathers >40 years of age. The literature demonstrates an association between APA and certain conditions including *de novo* autosomal dominant disorders, birth defects, and neuropsychiatric conditions. This study surveyed 165 genetic counselors within the National Society of Genetic Counselors to assess their current approach to APA. T-tests, analysis of variance, logistic regression, and Chi-squared tests were performed on quantitative data, and content analysis was applied to qualitative data. Although most respondents have discussed APA with a patient (88%), there was no consensus on what age cutoff constitutes APA: >40 (N=53, 37.9%), >45 (N=61, 43.6%), >50 (N=24, 17.1%), or >55 (N=2, 1.4%). Those who discussed APA were more likely to be prenatal counselors, see more patients per week, be board certified, or be familiar with current APA guidelines. Respondents agreed the literature supports the association of APA with deleterious outcomes (mean agreement = 8.2, median = 8 on a 1=strongly disagree to 10=strongly agree). Individuals who discussed APA and were board certified had higher agreement. Content analysis confirmed agreement that the literature supports an association between APA and deleterious outcomes (documented in responses from 31.5% of prenatal respondents, 17.8% others) but noted that available testing and screening options for associated conditions are limited (34.4% of prenatal respondents, 17.4% others). Prenatal and non-prenatal respondents reported similar agreement with the statement that APA is associated with deleterious outcomes. However, most non-prenatal respondents were unfamiliar with current guidelines (80%), and presumably as a result, were also less likely to discuss APA with their patients. Our study identified a need to disseminate information regarding APA and current guidelines to genetic counselors, particularly non-prenatal and those with less experience.

## Keywords

Advanced paternal age, genetic counseling, cell-free DNA, *de novo* mutation, prenatal diagnosis, attitudes

## Introduction

There is currently no consensus on the definition of advanced paternal age (APA). The American College of Medical Genetics utilizes >40 years of age (Toriello & Meck, 2008), as does a recently published review article describing the impact of advanced paternal age on reproduction (Brandt, Cruz Ithier, Rosen, & Ashkinadze, 2018). Regardless of the age threshold, studies have demonstrated negative effects of APA in various aspects of pregnancy and development. For example, data support a correlation between APA and increase in germline mutations, which are associated with an increased risk for specific genetic disorders (Wiener-Megnazi, Auslender, & Dirnfeld, 2012). An increase in DNA fragmentation incidence has been proposed as a mechanism for the increase in germline mutations, pregnancy loss, and infertility (Brandt et al., 2018; Rosiak-Gill et al., 2019). If pregnancy is achieved, the child is at risk of premature delivery, low birth weight, and decreased Apgar scores (Khandwala et al., 2018).

Of the reported risks with APA, increased risk for *de novo* autosomal dominant mutations has garnered the most attention. APA has been associated with children born with achondroplasia, thanatophoric dysplasia, osteogenesis imperfecta, Apert syndrome, Crouzon syndrome, Marfan syndrome, and neurofibromatosis (Nybo Andersen & Urhoj, 2017). According to a 2018 review published by Yatsenko and Turek, relative risk associated with APA for single gene mutations

ranging from pathogenic to benign is 10, and for rare single gene disorders, such as achondroplasia, ranges from 1.3-12 (Yatsenko & Turek, 2018). Some studies have suggested an increase in sex chromosome aneuploidy (De Souza & Morris, 2010; Slotter, Nath, Eskenazi, & Wyrobek, 2004) and neuropsychiatric conditions such as autism and schizophrenia (Foldi, Eyles, McGrath, & Burne, 2018; Greenberg et al., 2019; Mazur & Lipshultz, 2018; Nybo Andersen & Urhoj, 2017; Yatsenko & Turek, 2018). Given the increased risk of genetic mutations and the neurological conditions detailed above, should there be a consistent effort to discuss the effect of APA during genetic counseling sessions?

The most recent guideline regarding APA was published in 2008 by the American College of Medical Genetics (Toriello & Meck, 2008). This statement discusses treating pregnancies with fathers of APA as many other pregnancies are handled, and utilizing the 18-20 week ultrasound as a screening tool for significant birth defects. Prior to this statement the American College of Obstetricians and Gynecologists (ACOG) issued a statement in 1997 stating that “insufficient evidence exists to provide a specific cutoff level for assessing risk in association with paternal age” and genetic counseling was only recommended if a couple had specific concerns (ACOG Committee Opinion, 1997). A non-invasive prenatal screen was recently released which is being marketed as a screening tool for single-gene mutations in pregnancies with a father of APA. Initial data on 422 samples, 233 of which were available for post-natal follow-up, indicate a high positive predictive value. However, the reported average paternal age for the limited number of positive samples in this study was 36 years, below the typically utilized >40 cutoff for APA (Zhang et al., 2019).

The current but outdated practice guidelines include limited suggestions for how genetic counselors can best care for families where the father is of APA. In this study, we surveyed genetic counselors in North America from prenatal and other specialties in order to understand their current approach to discussing the risks of APA. By investigating current approaches, we can build upon a foundation to refine practice guidelines for these patients. The association between APA and specific conditions has been well-characterized. Utilizing this knowledge to enhance genetic counseling practices could improve patient care.

## **Methods**

### **Participants and Procedures**

The study protocol (#1804079251) was approved by the Indiana University Institutional Review Board (IRB). Participants in this study were members of the National Society of Genetic Counselors (NSGC) and were recruited through an NSGC email blast, which was distributed July 16<sup>th</sup> 2018 to 3,600 members of NSGC. A reminder email was distributed through the same system two weeks after initial email distribution. The survey remained open until August 14<sup>th</sup>, 2018. The survey was at least partially completed by 165 participants; not all participants completed the entirety of the survey.

### **Instrumentation**

The 25 question survey was developed through collaboration between authors, and was pilot-tested by two genetic counselors not involved with the study. The survey was developed in REDCap (Harris et al., 2019; Harris et al., 2009), and was divided into two sections: demographic questions and questions to address attitudes and current practice. Qualitative data

were collected through free response text and quantitative data were collected through yes/no, option choice, and Likert scale rating questions. No identifiable information was collected from the participants in order to ensure anonymity.

Demographic information included age, gender, practice specialty, years of practice, region of current practice, average number of patients per week, license, and certification status. Primary questions asked about specific attitudes and practices regarding APA. Specifically, age group considered to be APA (>35, >40, >45, >50, >55, or >60), discussion of APA with a patient (yes/no), offering screening (and options) on the basis of APA (yes/no), familiarity with APA guidelines (yes/no), and usefulness of updating the guidelines (yes/no). Of particular interest was agreement with the two statements asking about APA. The first inquired about the *link between APA and deleterious outcomes*: “*The body of currently published evidence establishes a correlation between advanced paternal age and certain genetic disorders, in particular de novo autosomal dominant mutations.*” Participants were asked to rate their agreement on a scale of 1 to 10, with 1 being strong disagreement and 10 being the strongest agreement. The second asked about *sufficiency of current guidelines* regarding APA: “*I feel the most recent guidelines on APA published by ACMG and ACOG are sufficient for guidance on how to best counsel for pregnancies with fathers of advanced paternal age.*” Potential responses were: agree, disagree, or unfamiliar with guidelines. This question was utilized as a covariate for the outcome variables detailed below and not as an outcome variable by itself. All survey questions and response options are available within the supplemental material.

## Data Analysis

Chi-squared tests were used to evaluate the association between categorical demographic questions and questions asking about attitudes and practice regarding APA, including APA age group, discussion of APA with patients, familiarity with APA guidelines, sufficiency of APA guidelines to guide genetic counseling, and the usefulness of updating current guidelines. Quantitative variables such as average number of patients per week, age, and years of practice were compared between demographic categories using a t-test or analysis of variance (ANOVA). Pearson's correlation coefficient was utilized to quantify associations between quantitative variables of interest. Logistic regression was employed to test if specialty, certification, length of practice, number of patients seen weekly, level of agreement that APA is linked to deleterious outcomes, sufficiency of current guidelines, or usefulness of updating guidelines were predictors of the binary outcomes: *discussion of APA with patients (yes/no)* and *familiarity with APA guidelines (familiar/unfamiliar)*. An ANOVA regression model was similarly employed for the quantitative variable: *agreement with the link between APA and deleterious outcomes*. For both analyses, all demographic variables were also included in the initial model. Due to associations between some of the demographic variables, the following interactions were also included as predictor variables in the logistic and ANOVA regression models: specialty (prenatal vs non-prenatal)\*years of practice, discuss APA\*board certification, and discuss APA\*average number of patients in models where the outcome was *not* one of the variables listed above. Variables with  $p < 0.10$  were retained for final models, in order to include all potential factors of interest.

Due to the small number of respondents in non-prenatal specialties, all specialties other than prenatal were combined into one category, such that specialty was coded as a binary variable: prenatal vs non-prenatal. Geographic locations were defined according to NSGC guidelines,

although regions 1 and 2 were combined to represent the broader northeast region, resulting in 5 geographic locations for analysis purposes. Only 5 participants (3%) reported they are not licensed to practice in their state which has licensure. For all analyses including the variable “license”, these individuals were coded as missing, due to the small number of individuals in this category. Non-board certified counselors could have different opinions on best practices regarding APA when compared to board certified counselors; therefore, board certification was included as a covariate of interest to identify this key issue in all appropriate analyses. Analyses were also re-run after excluding non-board certified counselor respondents (n=23) to ensure that results did not change. All statistical analyses were performed using SAS software v9.4 of the SAS system for Linux, Copyright 2016 by SAS Institute Inc., Cary, NC, USA.

Data analysis for free-response questions utilized inductive content analysis (Bengtsson, 2016; Elo & Kyngas, 2008; Patton, 2001). The first author examined all responses and identified common categories. Although an individual’s response was only counted once per category, the response could be included in multiple categories if it included multiple distinct ideas. For example, if a response to the question asking why a person would discuss APA with a patient read “If a man is 45 or older, if that is the reason for referral, or the patient brings it up.” This response would be included under categories of “The patient asks,” “Dad or sperm donor’s age,” and “Reason for referral.” New categories were included in the content analysis as they emerged. The second author (KAH) audited the original inductive content analysis and re-categorized as necessary. Discrepancies were discussed until an agreement was reached. Responses not relevant to the original question were excluded. From this data, frequencies within each category were calculated for prenatal and non-prenatal specialties. Representative responses were chosen if they



were common to 10% or more of respondents in either category. Any responses including test or company names were edited to use generic terms.

## **Results**

### *Demographics*

The email regarding the survey was delivered to 3,600 individuals, and had an open rate of 32.8%. The survey link itself was opened by 181 people. In total, 163 participants at least partially completed the survey for a response rate of 4.5% and 138 completed all survey questions. Demographic data was obtained on all 163, aside from one participant who did not report which NSGC practice region in which they currently practice. Of the participants, 49.7% were 29 years of age or younger, and around the same number had been practicing between 0-4 years. Due to the correlation between age and years of practice ( $r=0.91$ ,  $p<0.0001$ ), only years of practice was employed in subsequent analyses. The majority of the participants were female, which is representative of the genetic counseling field itself. Over half of the participants reported prenatal/preconception as their main practice specialty (64.4%), followed by pediatrics (15.9%). Most participants were board certified (85.9%), and slightly over half were licensed in their state (52.8%).

Summary demographic data are shown in Table I.

There was no association between geographical region and specialty ( $X^2(4)=2.0$ ,  $p=0.73$ ) or geographical region and years of practice ( $F(4,161)=2.05$ ,  $p=0.09$ ). Individuals in prenatal counseling had been practicing longer (8.6 years) than non-prenatal counselor respondents (4.8

years;  $t(161) = 3.0, p = 0.003$ ), saw more patients per week (15.4 vs 9.3,  $t(161) = 4.8, p < 0.0001$ ), and were marginally older (34.4 vs 31.4 years,  $t(161) = 1.9, p = 0.06$ ). Participants who were not board certified were significantly younger (26.8 years) compared to board certified respondents (34.4 years;  $t(161) = -3.6, p = 0.0004$ ), and consequently also had fewer years of practice (0.88 years vs 8.3 years,  $t(161) = -4.1, p < 0.0001$ ). There were no statistically significant associations between genetic counseling specialty and being board certified, licensed, or opinion regarding usefulness of updating the guidelines (all  $p > 0.21$ ).

#### *Definition of APA cutoff age*

Most participants indicated advanced paternal age to be  $>40$  ( $N=53, 37.9\%$ ),  $>45$  ( $N=61, 43.6\%$ ), or  $>50$  ( $N=24, 17.1\%$ ). Only two (1.4%) indicated  $>55$ , and were excluded from analyses including this variable. There was no association between genetic counseling specialty and APA cutoff age ( $X^2(2) = 0.32, p = 0.85$ ; excluding non-board certified  $p = 0.51$ ), board certification and APA cutoff age ( $X^2(2) = 2.1, p = 0.35$ ), or years of practice and APA cutoff age ( $F(2,137) = 1.19, p = 0.31$ ; excluding non-board certified  $F(2,119) = 1.17, p = 0.32$ ).

#### *Familiarity with APA guidelines (outcome variable)*

The most common responses to the question regarding *usefulness of updated guidelines* was being unfamiliar with current guidelines (50.0%, 69/138) or that updated practice guidelines are needed (23.2%, 32/138) in order to determine how they can best care for these patients. Logistic regression results showed that respondents who were prenatal counselors were 7.7 times more likely to be familiar with the guidelines (95% CI=(3.2, 18.6),  $p < 0.0001$ ). Specifically, 35.5% (33/93) of prenatal counselor respondents compared to 80.0% (36/45) of respondents in non-

prenatal specialties indicated they are unfamiliar with current professional guidelines regarding advanced paternal age. Similar results were obtained after excluding non-board certified respondents (34.9% prenatal and 80.6% non-prenatal,  $p < 0.0001$ ). Those who were in higher agreement that APA is linked to deleterious outcomes were marginally more likely to be familiar with current guidelines (OR=1.2, 95% CI=(0.97, 1.52,  $p=0.099$ ). There was no association with the remaining variables (all  $p > 0.35$ ).

#### *Discussing APA with patients (outcome variable)*

Most respondents reported discussing APA with a patient at some point (123/140, 87.9%), although the majority of those were prenatal counselors (90/123, 73.2%). In fact prenatal counselor respondents were 5.1 times more likely to discuss APA with their patients (95% CI=(1.4, 18.2),  $p=0.012$ ). However, after accounting for other factors in the logistic regression model, specialty was no longer a significant predictor of discussing APA ( $p=0.14$ ). Respondents who saw more patients per week (14.1 vs 8.1,  $p=0.038$ ), or were board certified (OR=4.6, 95% CI=(1.2, 17.9),  $p=0.025$ ), were more likely to discuss APA. Those who were familiar with the current guidelines were marginally more likely to discuss APA with patients (OR=4.8, 95% CI=(0.87, 26.3),  $p=0.071$ ). There were no other significant differences between those who discussed APA and those who did not for all other potentially confounding demographic variables (all  $p > 0.20$ ).

#### *Link between APA and deleterious outcomes (outcome variable)*

The mean response to the statement regarding the *link between APA and deleterious outcomes* was 8.1, median=8, SD = 1.7. The mean agreement among prenatal counselor respondents (mean=8.3, SD=1.6) was not significantly different from mean agreement among non-prenatal counselor respondents (mean=7.8, SD =1.8;  $F(1, 136)=2.6, p=0.11$ ). Although there was a positive correlation between length of practice and agreement rating ( $r=0.12$ ), this was not significant after accounting for other effects ( $F(1,136)=0.12, p=0.74$ ).

Respondents with higher mean agreement with the statement that there is a link between APA and deleterious outcomes indicated that updating APA guidelines would be useful ( $F(1, 136)=5.7, p=0.018$ ). Those who did not think the current guidelines were sufficient were in modestly but not significantly higher agreement ( $F(2, 136)=2.4, p=0.095$ ). The interaction effect of board certification and discussion of APA ( $F(1,136)=4.4, p=0.039$ ; Figure 1) revealed that among respondents who did not discuss APA, there was no difference in agreement ratings between those who were board certified compared to non-certified respondents (7.5 vs 8.1,  $p=0.91$ ). Among respondents who did discuss APA, those who were board certified had significantly higher agreement (mean = 8.8) compared to those who were not board certified (mean=7.4,  $p=0.02$ ). The main effect of being board certified was significant ( $F(1,136)=6.43, p=0.012$ ) before accounting for the interaction term but not after ( $F(1,136)=0.84, p=0.36$ ). Discussing APA with patients was not significant before ( $p=0.12$ ) or after accounting for the interaction ( $p=0.61$ ). No other variables or interactions predicted agreement rating on the link between APA and deleterious outcomes (all  $p>0.27$ ).

After removal of non-board certified respondents from the analysis, prenatal counselor respondents had significantly higher agreement (mean=8.4) than other specialties (mean=7.9,  $F(1,114)=5.4$ ,  $p=0.02$ ). In addition, the main effect of discussing APA with patients was marginal ( $p=0.053$ , mean rating of those who discussed APA=8.7,  $SE=0.23$  vs those who did not discuss APA=7.7,  $SE=0.54$ ). The p-value for agreement that updating guidelines would be useful was similar ( $p=0.023$ ).

#### *Testing or screening on basis of APA*

Overall, most respondents have not offered testing or screening on the basis of APA alone (90/139=64.8%; 72/119=60.5% excluding non-certified respondents). However, there was a significant association between prenatal vs non-prenatal specialties and whether or not they have offered testing or screening ( $X^2(1)=17.9$ ,  $p<0.0001$ ), which remained significant after removing non-certified respondents ( $p<0.0001$ ). More specifically, 47.3% of prenatal counselor respondents have offered testing on the basis of APA (44 offered testing, 49 did not), while the majority of non-prenatal counselor respondents reported they have not offered testing on the basis of APA (89.1%; 5 offered testing, 49 did not). Of the testing options provided, extensive ultrasound was most frequently selected (61.3%, 84/137) as the optimal test for APA-related conditions. The second most frequently selected option was point-mutation non-invasive prenatal screening, though this was only reported in 14.6% (20/137) of responses.

#### Content Analyses

Qualitative data were analyzed utilizing methods described above. There was no association of prenatal vs other specialties and board certification ( $X^2(1)=1.6$ ,  $p=0.21$ ); therefore all individuals

were included in the content analyses. When presented with the statement “Please explain reasons for why you would discuss advanced paternal age”, 26 categories were identified from 92 prenatal counselor respondents (87.6% of all prenatal counselor respondents) and 45 respondents from other specialties (77.6% of all respondents from other specialties) who provided responses which were placed into at least one category.

Categories which were represented by at least 10% of prenatal or other specialty respondents are presented in Table II. Responses of ‘not applicable’, ‘unaware of guidelines’ formed a separate category that is not included in these analyses. Approximately 32% (29/92) of prenatal counselor respondents reported that they “would discuss APA if the patient directly asked” or “they believe the literature supports a reason to discuss the risks”, compared to 13.3% (6/45) and 17.8% (8/45) responses placed into these two categories, respectively, of those in other specialties. The highest percentage of respondents in other specialties (22.2%, 10/45) had responses that were categorized as “a desire to fully inform the patient” and “using APA as an explanation for a differential diagnosis”. In comparison, 15.2% (14/92) and 3.3% (3/92) of prenatal counselor respondents provided responses categorized into these two categories. Interestingly, 19.6% (18/92) of prenatal counselor respondents and 17.8% (8/45) of those in other specialties provided responses categorized as “utilizing APA to normalize advanced maternal age and the associated risks”.

25 categories were identified from 90 prenatal counselor respondents (85.7% of all prenatal counselor respondents) and 46 respondents from other specialties (79.3% of all respondents from other specialties) who provided at least one reason to the prompt “Please explain reasons for why

you would not discuss advanced paternal age”. Categories and illustrative quotes representative of at least 10% of responses from either the prenatal or other specialties groups are displayed in Table III. Within both groups, the highest percentage of respondents (34.4% (31/90) of prenatal counselor respondents and 17.4% (8/46) of others) provided responses which were categorized as “limited available screening and testing options for conditions associated with APA”. The second most frequent category among prenatal counselor respondents (25.6%, 23/90) was that there are “more pressing concerns they needed to discuss with the patient”. For respondents in other specialties, the second most frequent category (15.2%, 7/46) was “not wanting to contribute to parental guilt or blame”; whereas, no responses from the prenatal counselor respondents fell into this category.

Thirteen categories were identified from 90 prenatal counselor respondents (85.7% of all prenatal counselor respondents) and 44 respondents from other specialties (75.9% of all respondents from other specialties) who provided at least one reason to the final prompt asking for reasons the respondents may or may not find updated guidelines regarding advanced paternal age helpful. Common categories and examples are presented in Table IV. For prenatal counselor respondents, the category with the largest number of responses (42.2%, 38/90) was that updated guidelines would be “useful due to the availability of new data and technology”. This category was present in responses of 18.2% (8/44) of non-prenatal counselor respondents. The responses of those in other specialties were most frequently categorized as “wanting guidance and recommendations in order to ensure consistency of practice” (41.0%, 18/44). This category was identified in 31.1% (28/90) of responses from prenatal counselor respondents. Though there was variability for the age which respondents use to define APA, only 12.2% (11/90) of prenatal

counselor respondents and 4.6% (2/44) of non-prenatal counselor respondents had responses which mentioned a desire to define the age for APA.

## **Discussion**

Numerous articles regarding data on APA have been published within recent years, including a recent review of APA (Brandt et al., 2018). However, this study is the first to examine the current approach of genetic counselors to APA in clinic. The most recent guidelines discussing APA and management recommendations were published in 2008 (Toriello & Meck, 2008), before the availability of new technology and genotyping techniques to screen for conditions linked to APA. Many participants indicated that they were unfamiliar with current guidelines, or that updated guidelines are necessary in order to improve the practice of genetic counseling. Even within the prenatal specialty, one-third of respondents reported they were unfamiliar with guidelines regarding APA. These results are a clear indication of the need to disseminate guidelines among all genetic counselors, including those in prenatal counseling. Furthermore, updating the guidelines to reflect new data and technologies would provide uniformity of genetic counseling practices, and could lead to improved patient care.

The majority of respondents reported discussing APA with a patient at some point in their practice. Prenatal genetic counselor respondents, respondents who were board certified, saw more patients, and had been practicing longer were more likely to have discussed APA with their patients. This identifies a demographic of genetic counselors who do not discuss APA, namely non-prenatal counselors and those who are newer to the field of genetic counseling. It is possible that people who do not report discussing APA do not do so because they are not familiar with the



guidelines, as these individuals were primarily non-prenatal counselors. When examining possibilities for why less experienced counselors tend not to discuss APA, a few explanations come to mind. Perhaps genetic counseling training programs do not incorporate APA as a topic of discussion, and therefore new graduates have not gathered enough confidence yet to branch away from their training. Alternatively, perhaps those with less experience are still refining and streamlining their practice, and lack time within a session to discuss something like APA. A category which emerged during content analysis revealed that time is a factor for the decision not to discuss APA with a patient. There are numerous other possibilities for examining this trend, and future studies could tap into reasons why more experienced counselors were more likely to bring up this sensitive topic. This further delineates a need to disseminate information about APA to genetic counselors outside the prenatal specialty and with less genetic counseling experience.

Our study also demonstrated the importance of being board certified relative to discussing APA. Those who were board certified were five times more likely to have discussed APA than those who were not, indicating a reluctance of non-board certified counselors to discuss APA. It is unclear from the current study why those who were not certified were less likely to discuss APA, but one hypothesis is that the lack of established credentials may result in a lack of confidence to discuss a non-clearly delineated topic such as APA. Those who are not certified were younger and had less experience. Non-certified counselor respondents indicated significantly lower agreement that there is evidence of a correlation between APA and deleterious outcomes compared to certified counselor respondents. Respondents who were not board certified *and* did not discuss APA had the *lowest* agreement that there is a correlation between APA and negative

outcomes. There is a clear indication that non-board certified counselors are not discussing APA with patients and are unaware of the negative impact that APA can have on pregnancy outcomes.

Though some respondents reported discussing APA with patients, there was no mutual agreement on what age defines APA. The fact that there was no clear age threshold identified by any of the demographic categories explored in this study suggests a lack of consistency among counselors. If genetic counselors are to be encouraged to discuss APA with their patients, a defined age is necessary to ensure uniform counseling across all patients. In fact, within the content analysis prompt regarding reasons why or why not respondents would find updated guidelines helpful, defining an age group was one of the categories identified in 12.2% of responses from prenatal counselor respondents. On the other hand, very few responded that having a defined age group would be helpful, which might reflect that counselors do have a personal definition of APA which they utilize in their practice. The current study demonstrated a lack of agreement regarding the cutoff age for APA, and perhaps future studies which delineate APA risks can assist in providing a clear, consistent APA cutoff age to be used by genetic counselors.

Overall, respondents tended to agree that the available literature supports a correlation between APA and genetic conditions, particularly *de novo* autosomal dominant mutations. Agreement of this statement was similar between prenatal vs non-prenatal respondents; however, non-prenatal respondents were significantly less likely to discuss APA with patients, and were more likely to be unfamiliar with guidelines. This identifies a gap in our field, and a need to provide additional information to non-prenatal counselors. Perhaps the lack of awareness and discussion is related

to how frequently APA is relevant to risk assessment and counseling their specific subset of patients. However, a number of the conditions associated with APA may not be diagnosed until the postnatal period and beyond, which would make knowledge of APA and associated risks relevant for those in non-prenatal specialties.

Respondents who had been in practice longer and felt current guidelines are sufficient had higher agreement with the statement regarding risks associated with APA. It seems a bit contradictory that though on average respondents agreed that there is a correlation of APA with deleterious outcomes, they were more likely to believe current guidelines are sufficient. The 2008 ACMG update to APA practice guidelines states, “There are currently no screening or diagnostic test panels which specifically target those conditions that increase with paternal age. If the older male’s partner is currently pregnant, the pregnancy should be treated as any other...” (Toriello & Meck, 2008). There are now available screening tests for some of the conditions associated with advanced paternal age. Though clinical validity data of these measures are still preliminary (ACOG, 2019; Zhang et al., 2019), it may be useful to revisit the guidelines and determine if additional recommendations regarding APA are warranted.

Prenatal counselor respondents and those in other specialties often differed in reasons why they would or would not discuss advanced paternal age with a patient. For prenatal counselor respondents, the most frequent categories for why they would discuss APA with a patient involved the patient directly asking and their belief that the literature supports a correlation between APA and multiple conditions, which was consistent with the quantitative data. For other specialties, the top reasons included fully informing the patients and using APA as support for a

differential diagnosis. These responses reflect how this topic relates to different specialties, and therefore responses are quite representative of those differences. Regarding reasons why they would not discuss APA, both prenatal counselor respondents and those in other specialties agreed that they are limited on available screening and testing options for conditions associated with APA. Single gene non-invasive prenatal screening is a relatively new technology, and the clinical utility within APA populations is still being investigated, since the only available study on its use was completed in a population which does not follow the most common definitions of APA (Zhang et al., 2019). While availability of this testing will not decrease the deleterious outcomes associated with APA, the increased discussions regarding APA during both pre- and post-test counseling will hopefully lead to a more uniform practice across genetic counselors.

With APA, there is documented association with neuropsychological conditions, which cannot be screened for on a prenatal test (Brandt et al., 2018; Mazur & Lipshultz, 2018; Yatsenko & Turek, 2018). If genetic counselors are discussing APA with patients, are they discussing this particular risk? Previous guidelines mention the correlations, but do not indicate how counselors should approach this issue. Respondents within this study indicated that they largely agreed with the literature published regarding conditions correlated with advanced paternal age. Further guidance on how they are to discuss these types of conditions, or whether they should be discussed at all, is needed. In future guidelines, governing bodies should put forth a concerted effort to ensure they are clear on when a discussion of APA should occur, and what aspects of APA are important to include in the discussion.

### **Study Limitations**

Despite the large sample size, there are some limitations to this study. This study focused on genetic counselors in North America only and thus the results may not be generalizable to counselors of other countries or cultures. Not all survey responses were completed, which led to a discrepancy between demographic data and data retrieved from open response questions. While some counselors from non-prenatal specialties responded, there were not enough respondents across other specialties to generalize to specific non-prenatal counseling settings. Some of the survey questions were ambiguous. Clearer delineation of topics such as “sufficiency” of current guidelines could help parse responses and clarify what is helpful and what is lacking in current guidelines. Furthermore, it would be helpful to know what genetic counselors do discuss with their patients regarding APA and what they omit during this discussion. Although the majority of cases with discussion about APA are seen in a prenatal setting, other practices such as pediatrics and psychiatric genetic counseling are likely to see such cases. Family practitioners and OB-GYN physicians may have patients that could benefit from discussion of APA, but were not included in the current study.

### **Research Recommendations**

This study is the first to examine the current approach taken by genetic counselors towards APA, which emphasizes the need for additional studies to delve into counseling for APA. For example, knowing topics of discussion within a session when APA is brought up could provide a more comprehensive look into how APA is being approached within the profession and help to update current guidelines. Additionally, there have been many recent analyses of published data on APA and newly acquired data regarding the use and utility of non-invasive screening methods targeting APA conditions is beginning to emerge (Zhang et al., 2019). In the present study,

respondents reported wanting updated guidelines due to advances in technology. Further delineation of utility of non-invasive screening measures within an APA-saturated population is needed. In order to better establish how genetic counselors can best care for patients where advanced paternal age is a concern, it is important to have data supporting or refuting the use of non-invasive screens specifically for advanced paternal age-related conditions.

### **Conclusion**

Multiple recent review articles have noted the association between APA and various conditions, including *de novo* autosomal dominant disorders, birth defects, and neuropsychiatric conditions (Brandt et al., 2018; Mazur & Lipshultz, 2018; Yatsenko & Turek, 2018). Despite recent advances in new technologies utilizing the cell-free fetal DNA technology to screen for some of the conditions associated with APA, the most recent practice guidelines regarding APA were last revised in 2008. Although further research is necessary to replicate these results, this study identified a need to recognize a uniform age to define APA, to increase awareness among genetic counselors of the risks associated with APA, and to more broadly disseminate guidelines for discussing the risks associated with APA, especially to non-prenatal genetic counselors and those with less experience. Updated guidelines which incorporate current data and technology could facilitate the practice of genetic counseling and assist in providing patients with uniform and comprehensive care.

### **Author Contributions**

Kayla Quirin conceptualized the idea for the study, created and interpreted study materials, and drafted and revised the manuscript.

Leah Wetherill assisted with formulation of the survey, completed all statistical analyses on the data, and assisted in drafting and revising the manuscript.

Karrie A. Hines assisted in establishing the idea for the study, assisted in formulation of study materials and survey, and revised the manuscript.

Authors Kayla Quirin and Leah Wetherill confirm that they had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

All of the authors gave final approval of this version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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### **Conflict of Interest**

Kayla Quirin, Leah Wetherill, and Karrie A. Hines have no conflicts of interest to disclose.

### **Human Studies and Informed Consent**

The study was approved by the Indiana University Institutional Review Board. No informed consent was required from subjects as data were anonymously extracted from REDCap. All procedures followed were in accordance with US Federal Policy for the Protection of Human Subjects.

### **Animal Studies**

No non-human animal studies were carried out by the authors for this article.

### **Data Availability Statement**

Data within this manuscript were collected by the authors and have not been shared. Data is available upon request to the corresponding author.



## Figure Legends

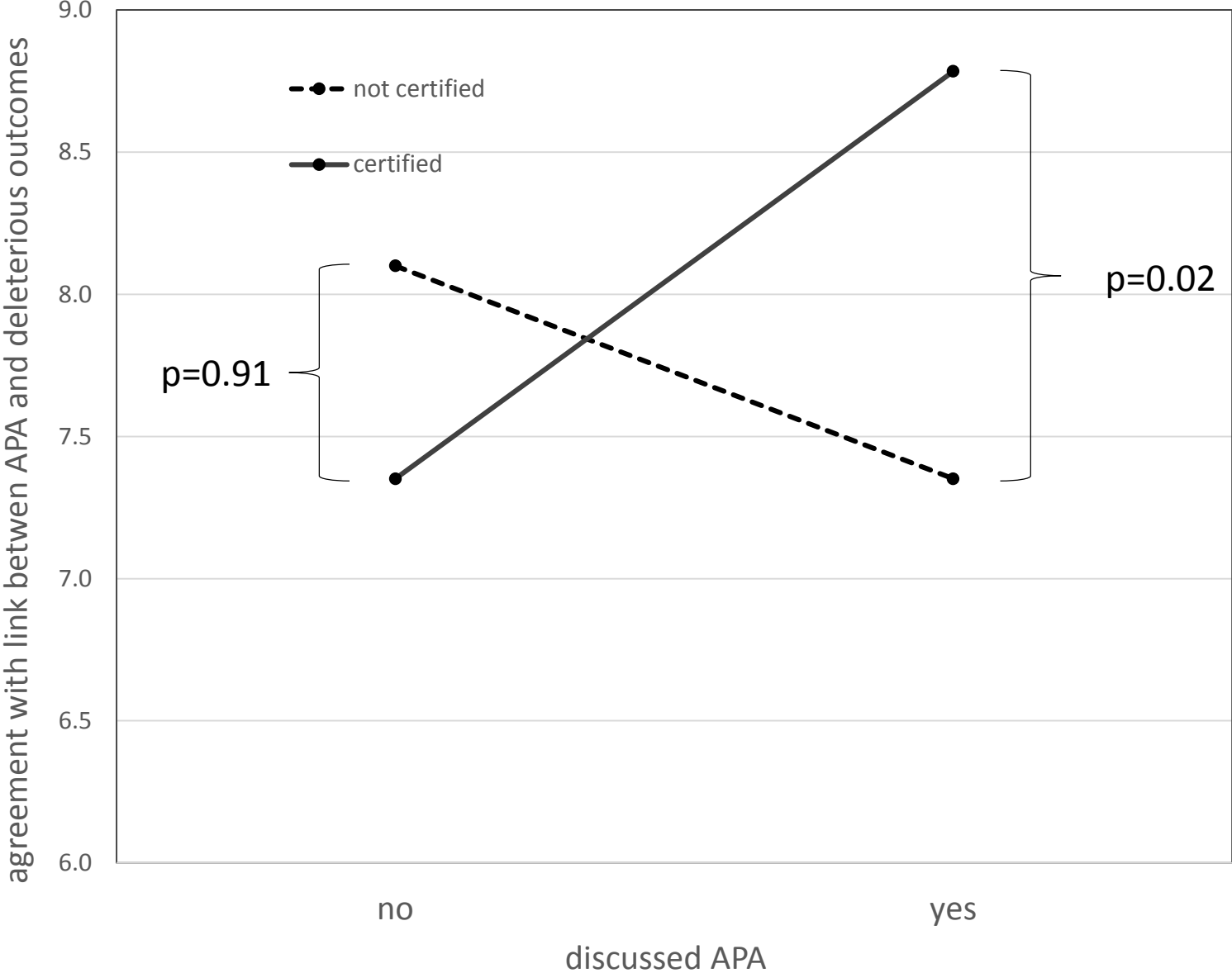
Figure 1: Interaction of board certification and discussion of APA predicts agreement with the question “*The body of currently published evidence establishes a correlation between advanced paternal age and certain genetic disorders, in particular de novo autosomal dominant mutations.*”

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Figure 1: Board Certification and Discussing APA Predict Agreement



# Current Practice of Genetic Counselors Regarding Advanced Paternal Age

The purpose of this research study is to investigate current practice of genetic counselors regarding their approach to advanced paternal age.

The survey is composed of two sections including questions which address demographic information and current practice towards advanced paternal age.

Taking part in the survey implies willingness to participate. There are no direct benefits for participating. However, your participation is contributing to the body of knowledge surrounding current approach within genetic counseling clinics. There is a risk of potential loss of confidentiality. All measures will be taken to protect your information. No identifiers will be recorded, and your responses will be coded. This survey has been reviewed in the exempt IRB process (protocol #1804079251). Participation is voluntary and no compensation is provided. The estimated time to complete this survey is 5-10 minutes.

Thank you in advance for taking the time to complete the survey below. If you have any questions or concerns, please contact genetic counseling student Kayla Quirin at [kquirin@iu.edu](mailto:kquirin@iu.edu)

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## The following questions are demographic based:

- 1 What is your age? \_\_\_\_\_  
Please enter an integer value between 1 and 100.
- 2 What is your gender?
  - Male
  - Female
  - Non-Binary
  - Prefer Not to Respond
- 3 What is your main practice specialty?
  - General
  - Pediatric
  - Prenatal
  - Cancer
  - Neurology
  - Cardiology
  - Metabolism
  - Other (Please specify)
- 4 Please specify your practice specialty if not included above. \_\_\_\_\_
- 5 How many years have you been a practicing genetic counselor? \_\_\_\_\_  
Please enter an integer value between 0 and 100.
- 6 What is the average number of patients you see per week? \_\_\_\_\_  
Please enter an integer value between 0 and 100.
- 7 Are you board certified?
  - Yes
  - No

- 8 Are you licensed to practice in your state?  Yes  No  My state does not license genetic counselors
- 9 Which NSCG practice region do you currently practice in?
- (Region I: CT, MA, ME, NH, RI, VT, CN, Maritime Provinces; Region II: DC, DE, MD, NJ, NY, PA, VA, WV, PR, VI; Region III: AL, FL, GA, KY, LA, MS, NC, SC, TN; Region IV: AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, WI, Ontario; Region V: AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Sask; Region VI: AK, CA, HI, ID, NV, OR, WA, British Columbia)
- I
  - II
  - III
  - IV
  - V
  - VI

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**The following questions address attitudes and current practice towards advanced paternal age. Please complete them to the best of your ability.**

- 10 What age group do you consider advanced paternal age?  >35  
 >40  
 >45  
 >50  
 >55  
 >60
- 11 Have you ever discussed advanced paternal age with a patient?  Yes  
 No
- 12 In a prenatal setting, would you discuss advanced paternal age with patients for which the father of the child is over 40 years old?  Yes  
 No
- 13 What percent of your practice includes fathers of advanced paternal age? \_\_\_\_\_  
Please enter an integer value between 0 and 100.
- 14 How strongly do you agree or disagree with the following statement? (10 strongly agree, 1 strongly disagree): "The body of currently published evidence establishes a correlation between advanced paternal age and certain genetic disorders, in particular de novo autosomal dominant mutations."  1  2  3  4  
 5  6  7  8  
 9  10
- 15 Please explain reasons for why you would discuss advanced paternal age.
- 16 Please explain reasons for why you would not discuss advanced paternal age.
- 17 Have you ever offered screening or testing options on the basis of advanced paternal age?  
 Yes  No
- 18 What testing or screening options do you currently offer for pregnancies with fathers of advanced paternal age?  
Please select all that apply.  
 Extensive ultrasound  
 Non-invasive prenatal screening  
 Point mutation non-invasive prenatal screening (such as Natera's Vistara screen)  
 Amniocentesis  
 CVS  
 Other  
 None of the above
- 19 If other, what screening or testing options do you offer?

- 20 What do you see as the optimal test or screen for pregnancies with fathers of advanced paternal age?
- Extensive ultrasound
  - Non-invasive prenatal screening
  - Point mutation non-invasive prenatal screening (such as Natera's Vistara screen)
  - Amniocentesis
  - CVS
  - Other
- 21 If other, what screen or test do you see as the optimal option?
- 
- 22 Are you familiar with the most recent guidelines from ACMG and ACOG on advanced paternal age?
- Yes
  - No
- 23 Do you agree or disagree with the following statement: "I feel the most recent guidelines on advanced paternal age published by ACMG and ACOG are sufficient for guidance on how to best counsel for pregnancies with fathers of advanced paternal age."
- Agree
  - Disagree
  - Unfamiliar with guidelines
- 24 Would you find updated guidelines on advanced paternal age useful?
- Yes
  - No
- 25 Referring to the previous question, why or why not?