

Statement on guidance for genetic counseling in advanced paternal age

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Disclaimer: This guideline is designed primarily as an educational resource for healthcare providers to help them provide quality medical genetic services. Adherence to this guideline does not necessarily assure a successful medical outcome. This guideline should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the geneticist should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from this guideline.

In 1996, a practice guideline on genetic counseling for advanced paternal age was published. The current document updates the state of knowledge of advanced paternal age effects on single gene mutations, chromosome anomalies, and complex traits. **Genet Med 2008;10(6):457–460.**

There is no clearly accepted definition of advanced paternal age. A frequently used criterion is any man aged 40 years or older at the time of conception. The current population mean paternal age is 27 years.

Advanced paternal age is associated with an increased risk of new gene mutations. Because of the large number of cell divisions during spermatogenesis, the mutation rate for base substitutions is much higher in men than women, and increases with paternal age. The risk for genetic defects increases linearly for some conditions, and exponentially for others.^{1–3} The conditions most strongly associated with advanced paternal age are those caused by mutations in the form of single base substitutions in the *FGFR2*, *FGFR3*, and *RET* genes, and include Pfeiffer syndrome, Crouzon syndrome, Apert syndrome, achondroplasia, thanatophoric dysplasia, as well as *MEN2A* and *MEN2B*.⁴ Some dominant conditions that are caused by gene changes that include both point mutations and base pair deletions (e.g., neurofibromatosis) show a lesser association with paternal age. Other dominant conditions show no association with increased paternal age.⁵ Although Friedman⁶ had estimated that the risk for autosomal dominant disorders af-

fecting offspring of fathers aged 40 or more was 0.3–0.5%, it is now thought that the actual risk is lower.⁷ There is also a growing body of evidence that advanced paternal age is associated with an increased risk for complex disorders such as some congenital anomalies, schizophrenia, autism spectrum disorders, and some forms of cancer.^{8–12} For most conditions the relative risk is two or less. However, the mechanism for the increased risk is unknown, and in some cases, the observed paternal age effect may be an artifact of some other causative factor.

In general, for autosomes and sex chromosomes, there is no compelling evidence that chromosomal aberrations (aneuploidy or structural chromosome abnormalities) are significantly increased in newborns as paternal age increases. The low incidence of paternally derived extra chromosomes in trisomies combined with the relatively small number of children fathered by older men makes it difficult to demonstrate a paternal age effect. Two possible exceptions are trisomy 21 and Klinefelter syndrome. Recent data on Down syndrome suggest a paternal age effect, either acting alone⁶ or in combination with a maternal age effect.^{13,14} This observation is supported by reports of increased aneuploidy rates in sperm for some of the chromosomes, including 21 and the sex chromosomes.^{15–17} In summary, there is a wide range of genetic disorders that may be related to advanced paternal age (Table 1). Overall, it seems that the risk of birth defects and some chromosome disorders may be minimally increased, and the risk for later onset disorders may also show a small increase with advanced paternal age. 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 according to pre-

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Table 1
Paternal age risks

Type	Specific condition	Age (relative to reference age)	Relative risk (CI, if available)	Population risk (or reference risk)	Adjusted risk	References (first author's name only)
Autosomal dominant	Achondroplasia	>50 (25–29)	7.8	1/15,000	1/1923	Risch ¹
		30–34 (<20)	3.5		1/4285	Tiemann-Boege ²¹
		35–39 (<20)	4		1/3750	
		40–44 (<20)	8		1/1875	
		45–49 (<20)	9		1/1666	
		50–54 (<20)	12		1/1250	
	Apert	>50 (25–29)	9.5	1/50,000	1/5263	Risch ¹
	Pfeiffer	>50 (25–29)	6	1/100,000	1/16,666	Glaser ²²
	Crouzon	>50 (25–29)	8	1/50,000	1/6250	
	Progeria	Unknown	Effect seen	“Exceedingly rare”		
	MEN2A	Unknown	Effect seen	1/30,000		
	MEN2B	Unknown	Effect seen	1/30,000		
	Neurofibromatosis I	>50 (25–29)	3.7 ^a	1/3000–1/4000	1/810–1/1080	Risch ¹
		>40 (<30)	2.9		1/1034–1/1380	Bunin ²³
	Osteogenesis imperfecta	>35 (<25)	2.5	1/10,000	1/4000	Carothers ²⁴
		>35 (<35)	1.37 (0.73–6.89)		1/7300	Orioli ²⁵
	Thanatophoric dysplasia	>35 (<35)	3.18 (1.48–6.89)	1/20,000–1/50,000	1/6290–1/15,723	Orioli ²⁵
	Retinoblastoma	>45	3 ^a (0.21–41.7)	1/15,000–1/20,000	1/5000–1/6667	Dockerty, Yip ^{26,27}
		>35 (<35)	1.34 (1.04–1.74)		1/11,200–1/14,925	Moll ²⁸
		>50 (32.5)	5		1/3000–1/4000	DerKinderen ²⁹
Chromosomal	Down syndrome	40–44 (20–29)	1.37 (0.48–3.86)	1/1200 (mat. age 20–29)	1/876	Zhu ³⁰
		45–49 (20–29)	2.68 (0.76–9.51)		1/448	
		>49 (20–29)	4.5 (1.0–20.3)		1/267	
		40–44 (25–29)	1.45 (1.26–1.68)	Use maternal age as baseline for counseling purposes ^b		Yang ³¹
		45–49 (25–29)	1.28 (1.04–1.57)			
		>49 (25–29)	1.39 (1.04–1.83)			
		None given	“May be increased”			Kuhnert ¹⁶
		None given	“Paternal age effect in association with maternal age (>35) effect”			Fisch ¹⁴
Congenital anomalies	Klinefelter syndrome	>50 (20's)	1.6 ^c (0.69–3.0)	1/500 men	1/312 men	Lowe ³²
	VSD	>40 (<40)	1.69 ^a	1/200	1/118	Olshan ³³
	ASD	>35	1.95 ^a	1/400	1/205	Lian ¹¹
	Tracheoesophageal fistula	>50 (25–29)	2.55 (1.28–4.6)	1/3600	1/1412	Yang ³¹
Other complex disorders	Childhood leukemia	>35	1.5	1/25,000	1/16,667	Murray ³⁴
		>40 (<25)	1.14 (0.85–1.53)		1/21930	Yip ²⁷
	Childhood CNS tumor	30–34 (<25)	1.34 (1.04–1.72)	1/36,000	1/26,866	Yip ²⁷
		35–39 (<25)	1.4 (1.04–1.86)		1/25,714	
		>40 (<25)	1.69 (1.21–2.35)		1/21,302	

(Continued)

Table 1
(Continued)

Type	Specific condition	Age (relative to reference age)	Relative risk (CI, if available)	Population risk (or reference risk)	Adjusted risk	References (first author's name only)
	Childhood type 1 diabetes	>34 (<25)	1.52 (1.1–2.09)	1/415	1/273	Cardwell ³⁵
	Epilepsy	35–39	1.18 (1.02–1.26)	1/100	1/85	Vestergaard ³⁶
		40–45	1.3 (1.08–1.55)		1/770	
	Schizophrenia	>50 (20–24)	4.62 (2.28–9.36)	1/100	1/22	Rasmussen ³⁷
		35–44 (15–24)	1.6 (1.0–2.6)		1/62.5	Zammit ³⁸
		45–54 (15–24)	1.6 (0.8–3.1)		1/62.5	
		>54 (15–24)	3.8 (1.3–11.8)		1/26	
		>49 (<25)	3		1/33	Malaspina ¹²
		>32 (<28)	3 (1.49–6.04)		1/33	Tsuchiya ³⁹
	Autism	>40 (<30)	5.75 (2.65–12.46)	1/1000	1/174	Reichenberg ⁴⁰
		Unknown	Effect seen			Cantor ⁹
	Autism spectrum disorders	35–39 (25–29)	1.38 (1.04–1.84)	1/200	1/145	Croen ⁴¹
		>39 (25–29)	1.52 (1.1–2.1)		1/131	
	Breast cancer	>40 (<30)	1.6 (1.04–2.32)	1/8.5	1/5.3	Choi ⁴²
	Prostate cancer	>38 (<27)	1.7 (1.0–2.8)	1/5.9	1/3.5	Zhang ⁴³
	Multiple sclerosis	51–55 (21–25)	2.0 (1.35–2.96)			Montgomery ⁴⁴
Other	Spontaneous miscarriages	>35 (<35)	1.26 (1.0–1.6)	1/7	1/5.3	Slama ⁴⁵
		>39 (25–29)	1.6 (1.2–2.0)		1/4	Kleinhaus ⁴⁶
	Relative infertility	>39 (<39)	2.3 (1.67–3.17)	1/14 couples	1/6.2	De la Rochebrochard ⁴⁷
	Low birth weight	>34 (20–34)	1.7 (1.3–2.2)	1/40	1/23	Reichman ⁴⁸
	Preeclampsia	35–44 (25–34)	1.24 (1.05–1.46)	1/62	1/50	Harlap ⁴⁹
		>44 (25–34)	1.8 (1.04–1.51)	1/62	1/34	
Total risk	For 86 examined congenital anomalies	>40 (<20)	1.2	1/50	1/42	Lian ¹¹
		>50 (<20)	1.3		1/38	

This table is meant to show the findings of various studies examining the effect of paternal age on the condition in question. It is not meant to be a comprehensive guide to counseling, but to merely indicate conditions which have been studied and results obtained from those studies.

^aIncreased risk not shown by other studies.

^bSuggestion for this adjustment made by the author of this document. There are no data regarding use of paternal age for counseling for serum screening results.

^cBased on frequency of XY sperm.

natal diagnosis guidelines established by the American College of Medical Genetics and American College of Obstetricians and Gynecologists,^{18–20} with the prenatal counseling session including a discussion about the potentially increased risk of Down syndrome attributable to increased paternal age. Because of this and the possibility of ultrasound detection of some of the features of the autosomal dominant conditions noted above (e.g., thanatophoric dysplasia), an ultrasound is recommended at 18–20-weeks gestation to evaluate fetal growth and development. However, it is unlikely to detect many of the conditions of interest. Prospective couples should receive individualized genetic counseling to address specific concerns.

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