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To Whom It May Concern,

I am the current Editor-in-Chief for the NIH-supported genetics website *GeneReviews*, an international point-of-care resource for busy clinicians that provides clinically relevant and medically actionable information for inherited conditions in a standardized journal-style format, covering diagnosis, management, and genetic counseling for patients and their families. We currently have more than 930 posted chapters on rare genetic conditions and had more than 10 million visitors to our website in 2024.

A number of genetic conditions represented in *GeneReviews* are inherited in an X-linked manner. In the past, X-linked conditions were further separated into "X-linked recessive" and "X-linked dominant" subcategories, denoting whether the classic features of the condition primarily affected genetic males or genetic females. However, this subcategorization is a misnomer that does not typically reflect the reality of these conditions in a clinical setting. As such, about 20 years ago, *GeneReviews* stopped using these subcategorizations and instead adopted the term "X-linked" (without further stratification) to represent these conditions. The main reasons for this are listed below.

- Most genetic conditions that are inherited in an X-linked manner actually affect both genetic males and genetic females, frequently in different ways, which have different medical implications based on genetic sex. For example, many genetic females who have heterozygous pathogenic variants in *DMD* do not have classic Duchenne muscular dystrophy (as is found in genetic males), but they do have associated health complications that require further health surveillance and management. Specifically, these women are at increased risk of developing cardiomyopathy in adulthood. By using the term "X-linked recessive" in conjunction with this condition, the implication is that females who have a heterozygous pathogenic variant in *DMD* will not have any features and will remain asymptomatic throughout their lives. This is a detrimental and erroneous assumption. As such, use of "X-linked recessive" terminology for this condition is not just an error in semantics but it can have real-world consequences for females who might not receive the appropriate surveillance and health care.

- In some X-linked conditions, genetic females may have features that actually are quite similar or the same as genetic males. This may depend on a number of factors. One such factor is that genetic females typically have one active X chromosome in each cell, with the other X inactivated. If the active X chromosome in a vast majority of cells (or in a majority of cells in a relevant organ) have the pathogenic genetic change, then that genetic female will have similar or the same features as genetic males. By glossing over the possibility

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that genetic females who are heterozygous for an X-linked condition can actually have the condition, we are doing a disservice to these females and risk disregarding their condition or misdiagnosing them with something else. This negatively impacts patient care and can lead to increased health care costs, particularly if a misdiagnosis leads to inappropriate treatment.

- The term “X-linked recessive” also implies that a heterozygous female is a “carrier” of a condition. This is erroneous. In autosomal recessive conditions, the term “carrier” implies that a person will never have symptoms related to their carrier status and the only risk is with regard to reproductive risk. Again, this glosses over the actual health risks associated with X-linked conditions in heterozygous females.

For these reasons we are urging ALL resources that reference or include X-linked conditions to similarly drop the terms “X-linked recessive” and “X-linked dominant” and their erroneous implications for the health of individuals with heterozygous or hemizygous pathogenic variants in X-linked genes. Instead, the term “X-linked” without further subcategorization should be used.

Sincerely,

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