ADDENDUM | Genetics inMedicine

**Focused Revision:** ACMG practice resource: Genetic evaluation of short stature

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Addendum to: "ACMG practice guideline: Genetic evaluation of short stature". Laurie H. Seaver, MD and Mira Irons, MD; ACMG Professional Practice and Guidelines Committee *Genetics in Medicine* 11:465–470 (2009); https://doi.org/10.1097/GIM.0b013e3181a7e8f8; published online 02 April 2009.

This document was reaffirmed by the ACMG Board of Directors as of 27 October 2020 with the following addendum as a Focused Revision:

We conducted a comprehensive search of the literature published between 2009, when the previous guidelines were published, and May 2020. Keywords used in PubMed included "short stature," "genetic evaluation," "short stature microarray," "short stature exome sequencing" using [All Fields] [TITLE-ABS-KEY] criteria. A total of 583 articles were found of which 539 primarily addressed the identification of genes associated with growth and gene defects associated with short stature. There were 44 articles regarding the genetic evaluation of short stature. We reviewed these articles and provide the following focused revision to the original document.

1. We have updated the previously published algorithm for the genetic evaluation of short stature[1] (Fig. **1**) with the following alterations:
   a. Girls who show persistent or evolving short stature in childhood should have a karyotype included in their initial short stature/failure-to-thrive work-up as screening for Turner syndrome, which is often delayed until adolescence,[2] resulting in missed opportunities for condition-specific interventions. A referral to endocrinology should be considered in early childhood, because a sex bias in short stature referrals has been found.[3] In girls with persistent or evolving short stature, microarray would be indicated if Turner syndrome has been excluded.
   b. Chromosomal microarray (comparative genomic hybridization [CGH] and/or single-nucleotide polymorphism [SNP]) should be part of the initial genetic work-up for idiopathic short stature (ISS) and small for gestational age (SGA) with persistent short stature as well as syndromic short stature, since the yield of pathogenic and likely pathogenic copy-number variants (CNV) was reported as high as 10% in this population in one study.[4] Multiple studies have reaffirmed use of microarray as first-line testing in patients with syndromic short stature with an average yield of 10–15%.[5–8] It is important to note that SNP-based chromosomal microarray can document uniparental isodisomy, but not uniparental heterodisomy or methylation patterns.[9,10] Therefore, further specific methylation or uniparental heterodisomy testing should be considered for any condition related to methylation defects (e.g., Silver–Russell syndrome, Temple syndrome).
   c. Rapid technological development has led to the discovery of an increasing number of novel genetic causes for short stature. Multiple genes that cause skeletal dysplasia have been implicated in cases of ISS and SGA with persistent short stature. Several genes associated with endocrinopathies, such as the growth hormone (GH)-insulin-like growth factor-1 (IGF-1) axis syndromes, have also been observed in children with ISS.[11–21] Therefore, clinical phenotypes of short stature-associated syndromes are expected to expand, and molecular testing for children with short stature should be considered (particularly *SHOX*) even without overt signs of skeletal dysplasia or endocrinopathy.[22,23]
   d. Clinicians should explore the yield and other limitations of individual next-generation sequencing (NGS) panels and array technologies based on the data from the laboratory offering the testing. Clinicians should be aware of difficult-to-sequence regions, including genes located in highly homologous and repetitive regions.[24] For example, the *SHOX* and *GH1* genes are located in segmental duplication regions and NGS has a limited coverage and detection limitations.
   e. Further testing with clinical exome sequencing and referral to medical genetics should be considered for patients with the following features suggestive of a monogenic cause for short stature: significant short stature (height < -3 SD), facial dysmorphism, skeletal abnormalities, intellectual disability, microcephaly, multiple pituitary hormone deficiency, severe growth hormone deficiency, SGA with persistent short stature, family history of consanguinity, or family history of one parent

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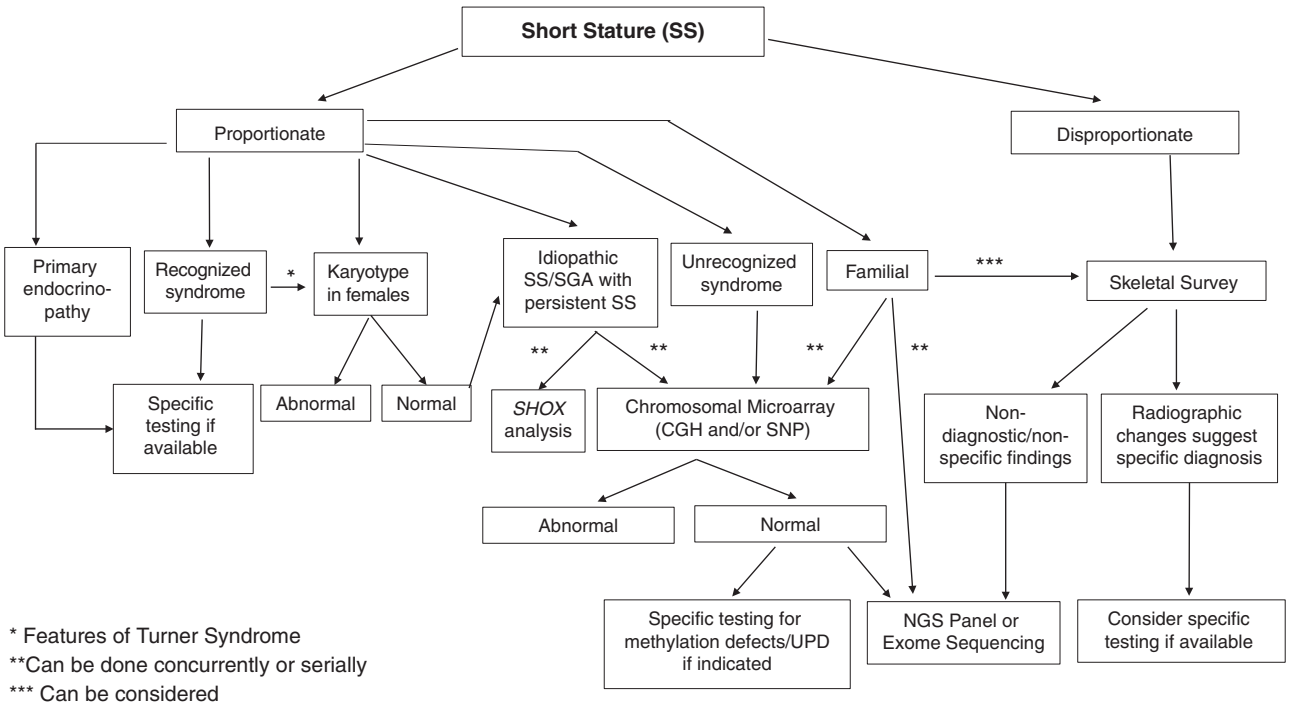


**Fig. 1** Algorithm for the genetic evaluation of short stature.

with height < -2 SD.[25–28] Current studies assessing diagnostic yield of exome sequencing for syndromic short stature with prior negative karyotype, microarray and NGS targeted panels is reported between 16.5% and 46%.[29–32] Clinical genome sequencing has begun to be offered in select laboratories and can be considered if available. At this time, important considerations include the cost of this testing, insurance reimbursement, and lack of evidence that clinical genome sequencing has a significantly increased diagnostic yield compared with clinical exome sequencing.[33] Additionally, clinical genome sequencing has not been studied specifically in any short stature cohort in the literature.

f. Important resources for clinicians to utilize in the evaluation and management of patients with a genetic diagnosis that includes short stature include disease-specific growth charts (which can be found on CDC.gov or disease-specific organization websites), GeneReviews® and the ACMG and American Academy of Pediatrics (AAP) practice guidelines.

2. Because the ACMG 2009 short stature document[1] does not meet the criteria for an evidence-based practice guideline by the ACMG (2014), it is now reclassified as a Clinical Practice Resource.

## DISCLOSURE

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