46,XY DSD
Partial Gonadal Dysgenesis

Presented by Kessanee Romphothong, MD
Supervised by Pichaporn Phudphong, MD
Wiwat Rodprasert, MD

Endocrinology and Metabolism Unit
Faculty of Medicine, Vajira Hospital
Navamindradhirad University

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46,XY DSD Gonadal Dysgenesis

- Impaired development of the gonads
- Begins early either at fertilization or shortly after in the early stages of the embryo and fetus
- Genetic diagnosis is currently reached in only about 20% to 40%

➢ **Complete gonadal dysgenesis** = Swyer syndrome

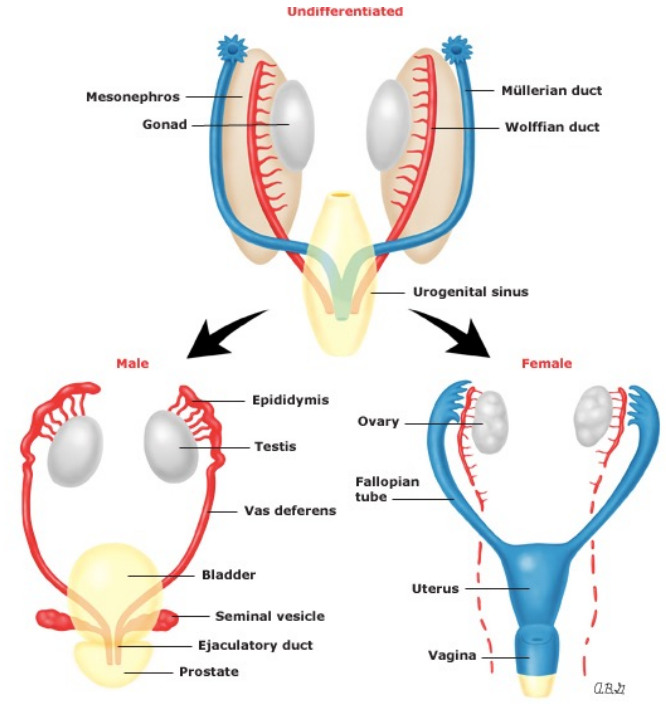
➢ **Partial gonadal dysgenesis**

- Mutations and deletions in SRY (10-20%)
- Mutations of NR5A1 (9q33)
- Mutation of DHH (12q13.1)
- In most cases → Unknown mutation

Adapted from Bulun SE. Williams Textbook of Endocrinology 14^{th} Edition page 890
Maciel-Guerra AT, et al. Fertil Steril. 2011 Dec;96(6):1431-4.

Complete VS Partial Gonadal Dysgenesis

	Complete Gonadal Dysgenesis (Swyer syndrome)	Partial Gonadal Dysgensis
Gonad	Streak/Dysgenetic gonad	
Internal genital organ	Persistant of mullerian structures	Vary +/- uterus +/- upper of vagina +/- male internal structures
External genital organ	Female external genitalia	- Clitoromegaly - Ambiguous genitalia - Isolated hypospadias
AMH	Insufficient	Vary



In typical XX individuals, the müllerian ducts give rise to the fallopian tubes, uterus, and upper vagina and the Wolffian ducts persist in vestigial form. In typical XY individuals, the Wolffian ducts give rise to the epididymides, vasa deferentia, seminal vesicles, and ejaculatory ducts and the müllerian ducts regress.

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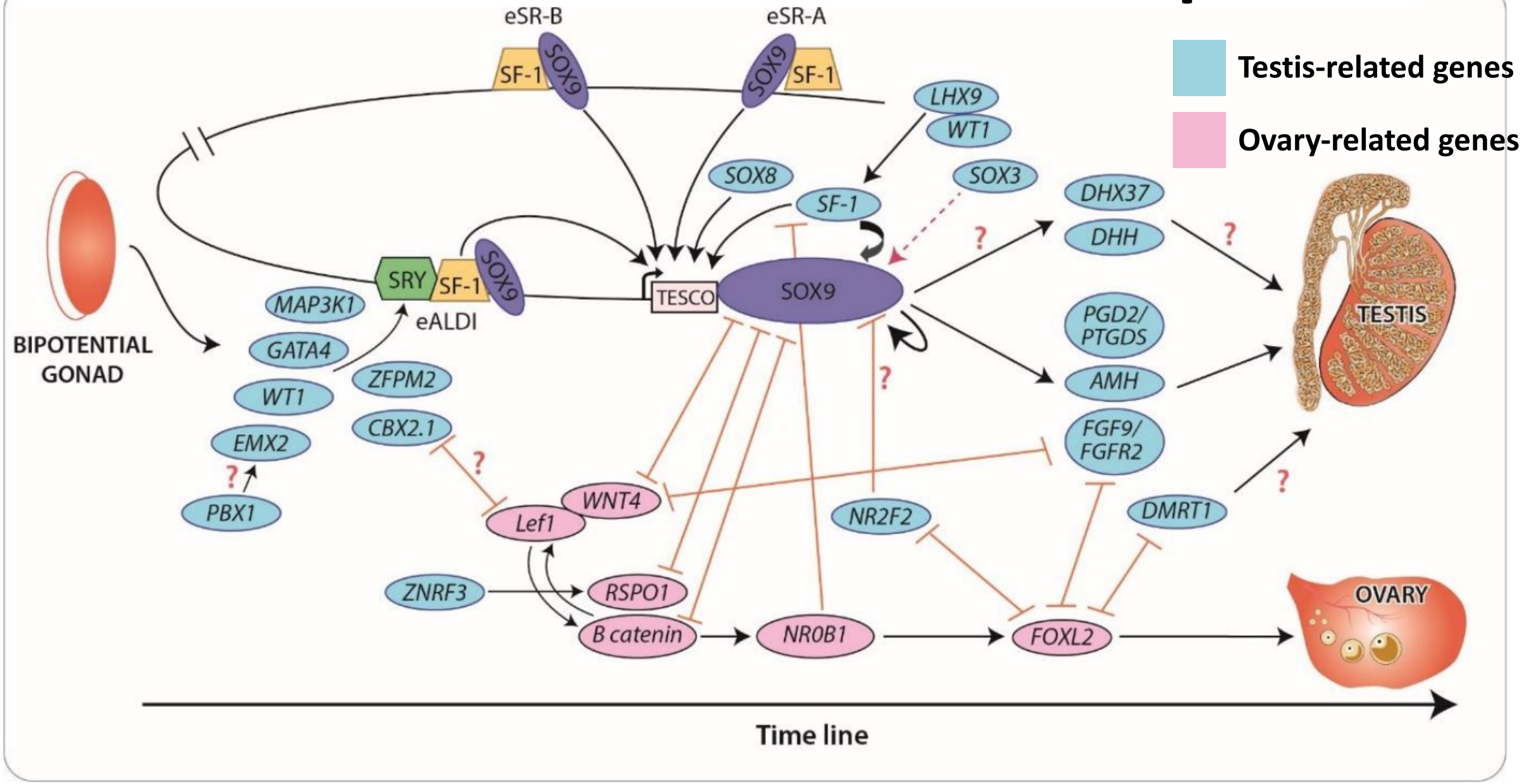
Genes Involved in Gonadal Development



Gomes NL, Chetty T, Jorgensen A, Mitchell RT. Disorders of Sex Development-Novel Regulators, Impacts on Fertility, and Options for Fertility Preservation. Int J Mol Sci. 2020 Mar 26;21(7):2282.

Patients with suspected XY-Partial gonadal dysgenesis
based on history and physical examination

- **Genetic Testing**
  - **Chromosomal analysis** (karyotype & array CGH*)
  - **FISH for SRY**
  - If SRY is present and chromosome analysis and array CGH are normal
    → **Sequence analysis** for **SRY, NR5A1, and DHH**
    - If these sequences are normal
      - Verify coverage of **NR0B1** and **WNT4** on array CGH testing
      - If not well covered, targeted duplication analysis may be considered
  - **Surgical Management**
- **Hormonal Evaluation**
- **Imaging**

*Array CGH = Array comparative genomic hybridization (CGH) analysis

McCann-Crosby B, et al. State of the art review in gonadal dysgenesis: challenges in diagnosis and management. Int J Pediatr Endocrinol. 2014;2014(1):4.

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Surgical Management

Hormonal Evaluation

Imaging

If other syndromic features are noted on physical exam, specific genetic testing should be sent:
- **SOX9 sequencing** if patient has finding consistent with **campomelic dysplasia**
- **ARTX sequencing** if patient has evidence of **alpha-thalassemia X-linked mental retardation**
- **WT1 sequencing** if patient has findings consistent with Denys-Drash

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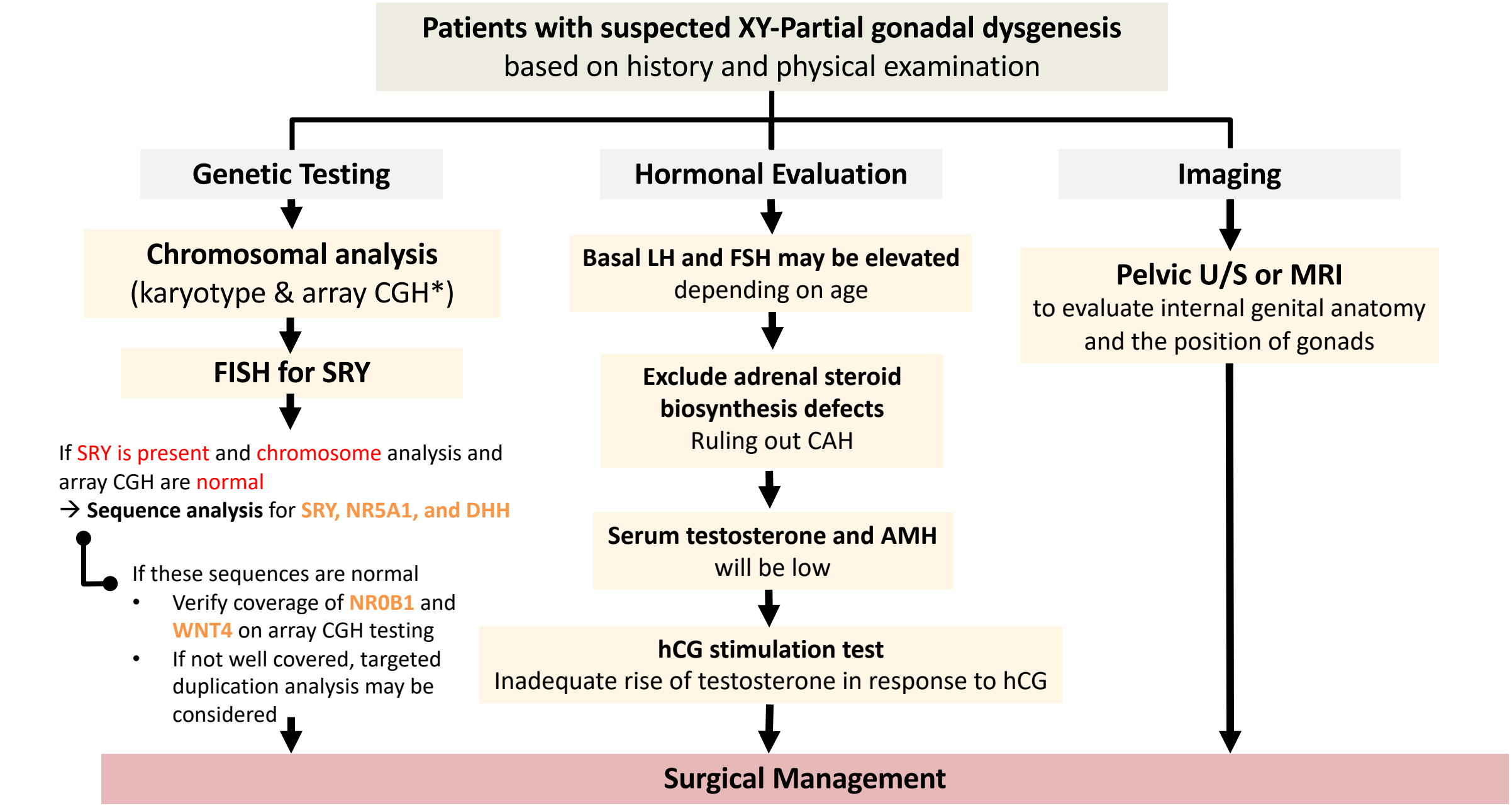

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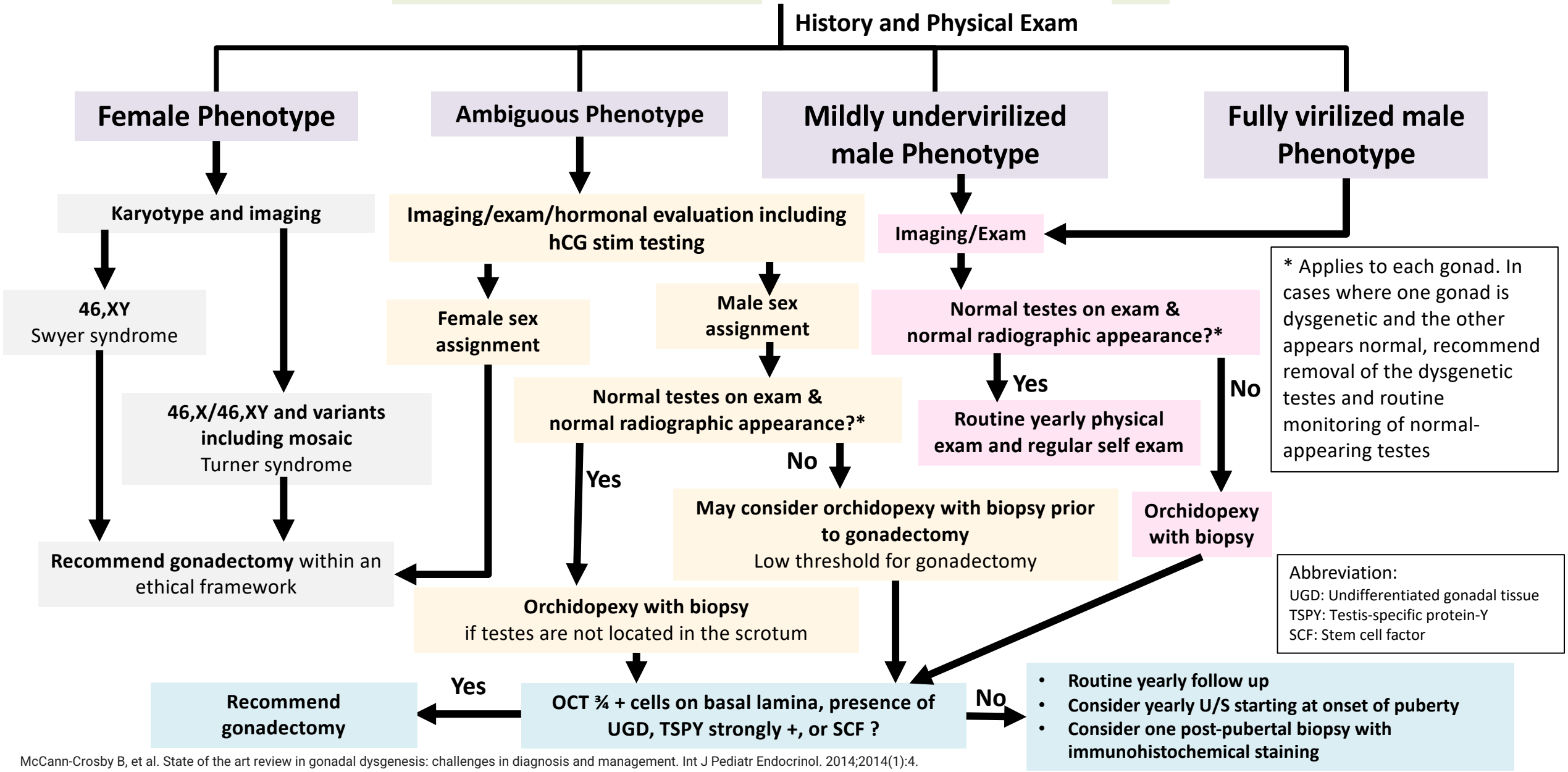
Diagnostic Algorithm and Management for Patients with Confirmed XY Gonadal Dysgenesis



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