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Male infertility

Causes and risk factors of testicular failure and genital tract abnormalities

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Congenital

Klinefelter's syndrome and variants
Male XX syndrome
Robertsonian translocation/inversions
Y chromosome microdeletions: partial and complete
Cystic Fibrosis
Novel monogenic mutations, eg, TEX11
Immotile cilia/Kartagener's syndrome
Congenital cryptorchidism

Acquired

Infections, eg, mumps orchitis, echovirus, gonorrhea, chlamydia
Infiltrative disease, eg, TB
Testicular torsion or trauma or malignancy
Chemotherapy, pelvic irradiation, or surgery
Large varicoceles
Medications

Idiopathic

Environmental factors/systemic disease

Obesity
Endocrine-disrupting chemicals
Lifestyle factors, eg, alcohol, smoking, recreational drug use

Genital tract abnormalities (defect in sperm transport)

Obstruction: congenital absence of vas deferens, infections, vasectomy
Others: ejaculatory dysfunction

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Sharma, A., Minhas, S., Dhillo, W. S., & Jayasena, C. N. (2021). Male infertility due to testicular disorders. The Journal of Clinical Endocrinology & Metabolism, 106(2), e442-e459.

How to approach male infertility

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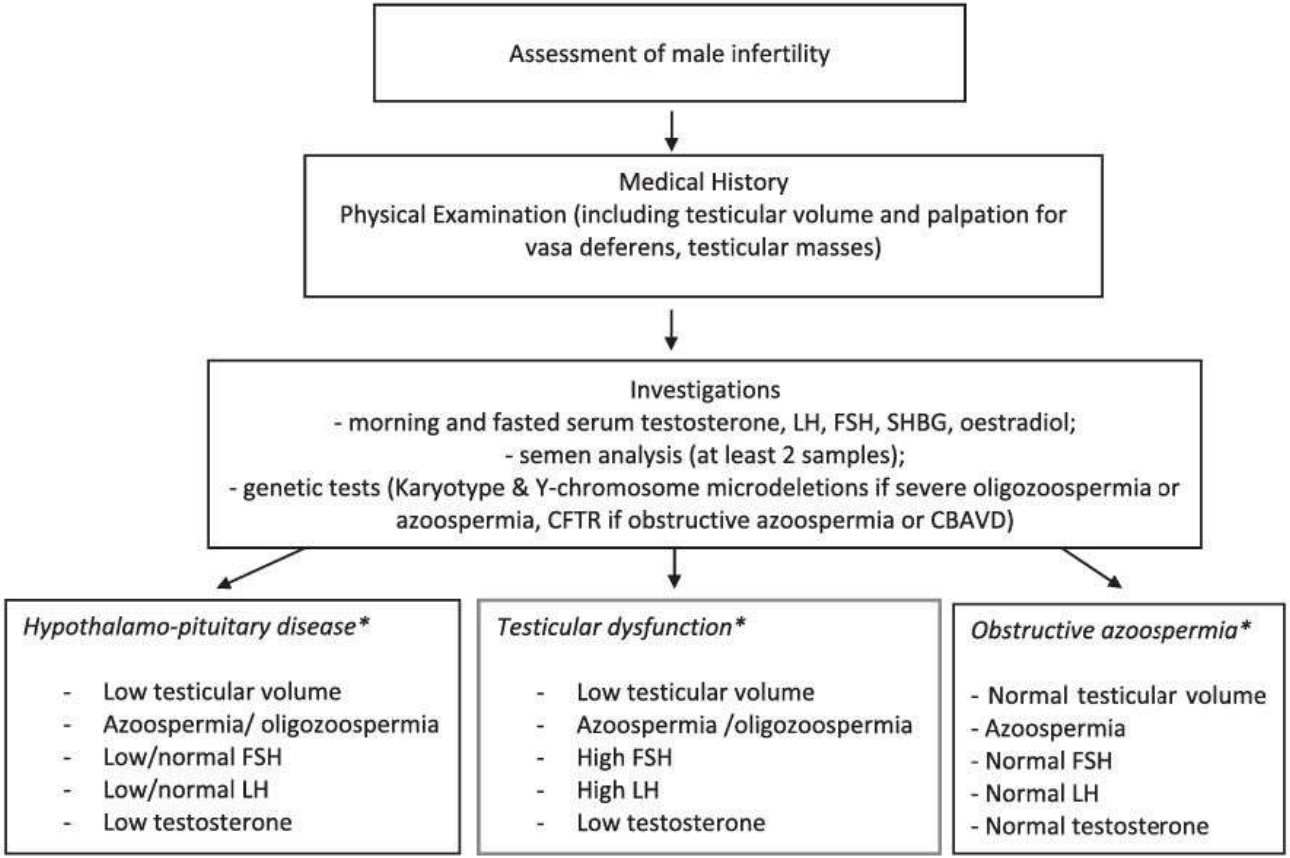

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Sertoli cell-only syndrome (SCOS)

Diagnosis & clinical management

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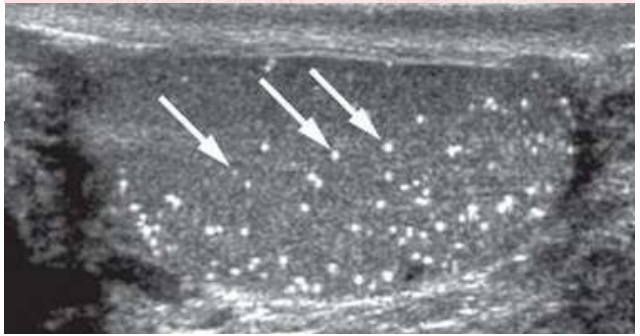
Clinical Features

- **Phenotype:** Normal virilization (Exception: Klinefelter syndrome)
- **Physical Exam:** Small testes

Testicular Ultrasound

- **Primary goals:** Assess testicular volume and check for microlithiasis.

MICROLITHIASIS = Associated with elevated tumor risk.



Laboratory Tests

Semen analysis (repeated twice, 90 days apart)

Hormones:

- FSH ↑
- Inhibin B ↓
- LH normal or ↑
- Testosterone normal or ↓

Definitive Diagnosis
(Histology)

Testicular Biopsy is the **Gold Standard** for SCOS diagnosis.

Eugeni, E., Arato, I., Mancuso, F., Brancorsini, S., Luca, G., & Kofler, S. (2025). Sertoli cells-only syndrome: current clinical approaches and ongoing research trends. Frontiers in Endocrinology, 16, 1715642.

Genetic Etiologies

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1. Chromosomal abnormalities

- Klinefelter syndrome (47,XXY)

2. Y-Chromosome Microdeletion

- *AZF* (Azoospermia factor region)
  - *AZFa* deletion
  - *AZFb* deletion
  - *AZFc*

3. Single-Gene Mutations Affecting Spermatogenesis

- Androgen signaling
  - *AR* (Androgen receptor)
- Germ cell differentiation
  - *DMRT1*
- Gonadal development / steroidogenesis
  - *NR5A1* (SF-1)c deletion

4. Sertoli–Germ Cell Signaling Defects

- *ETV5*
- *GILZ*
- *FGF9*

5. Hormonal Signaling Abnormalities

- *FSHB mutation*
- *FSHR mutation*

6. Cryptorchidism-Related Genetic Factors

- INSL3 mutation
- LGR8 (GREAT) receptor mutation

Genetic testing

(including but not limited to)

a. Karyotype analysis

b. Y chromosome microdeletion screening

c. Whole exome sequencing (WES)

Valdes-Socin, H., Parisel, A., Coppens, L., Henry, L., Gaspard, O., Sempels, M., & Petrossians, P. (2026). Sertoli cell-only syndrome (Del Castillo syndrome): Past, present and future. Annales D Endocrinologie, 87(1), 102481.

Clinical Diagnosis & Histological Variations

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TESTICULAR BIOPSY: THE GOLD STANDARD

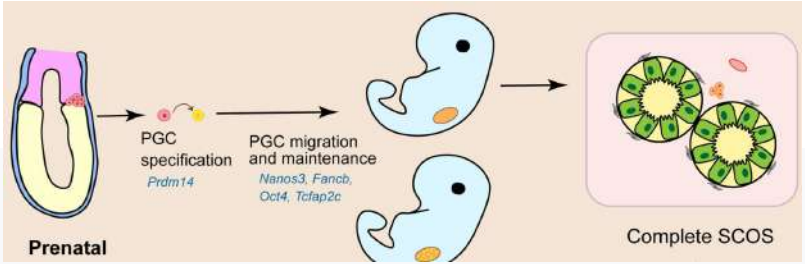
Definitive diagnosis requires histological confirmation of seminiferous tubules populated exclusively by Sertoli cells

Primary (Complete, cCOS)

ETIOLOGY

Prenatal failure in gonocyte migration

- Immature Sertoli cell phenotype
- Ovoid-rounded nuclei



Secondary (Incomplete, iSCOS)

ETIOLOGY

Acquired: Chemotherapy, radiation, or trauma

- Irregular nuclei
- Peri-tubular fibrosis & thickened basement membranes

May retain focal areas of spermatogenesis

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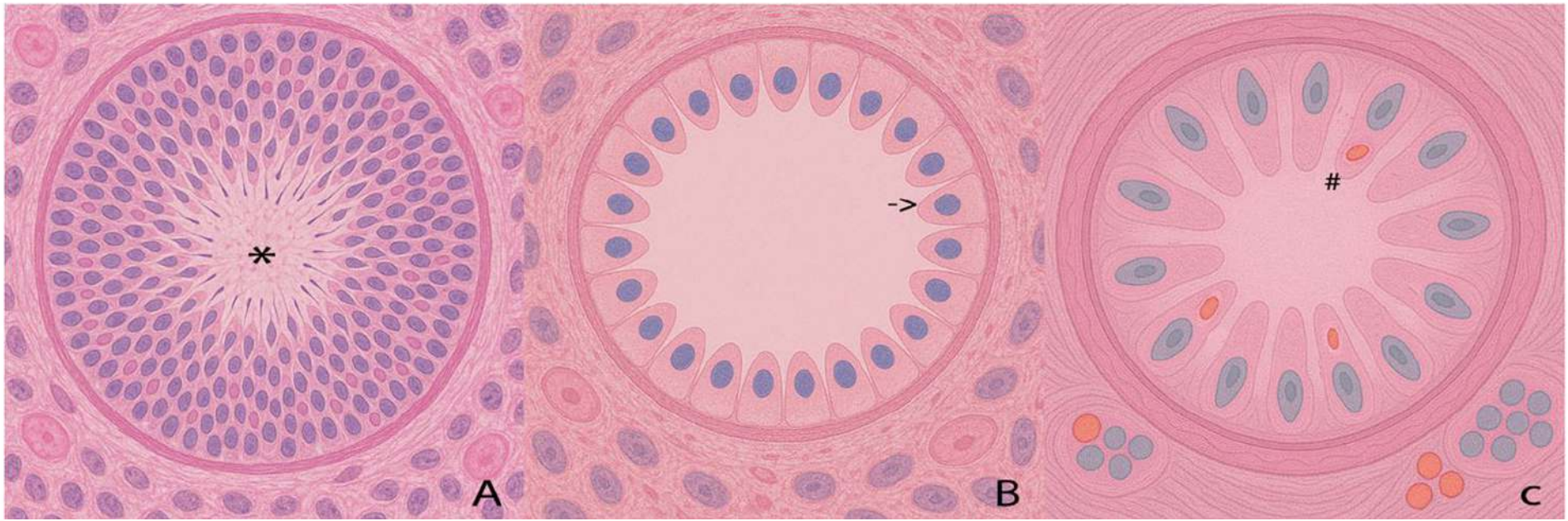

- Normal seminiferous tubule
- Germ cells in different stages of spermatogenesis which occur in spiral pattern

- Primary SCOS
- Classic ovoid nuclei of immature sertoli cells
- Normal thickness of the basement membrane

- Secondary SCOS
- Thickening basement membrane
- Intracellular lipid vacuoles

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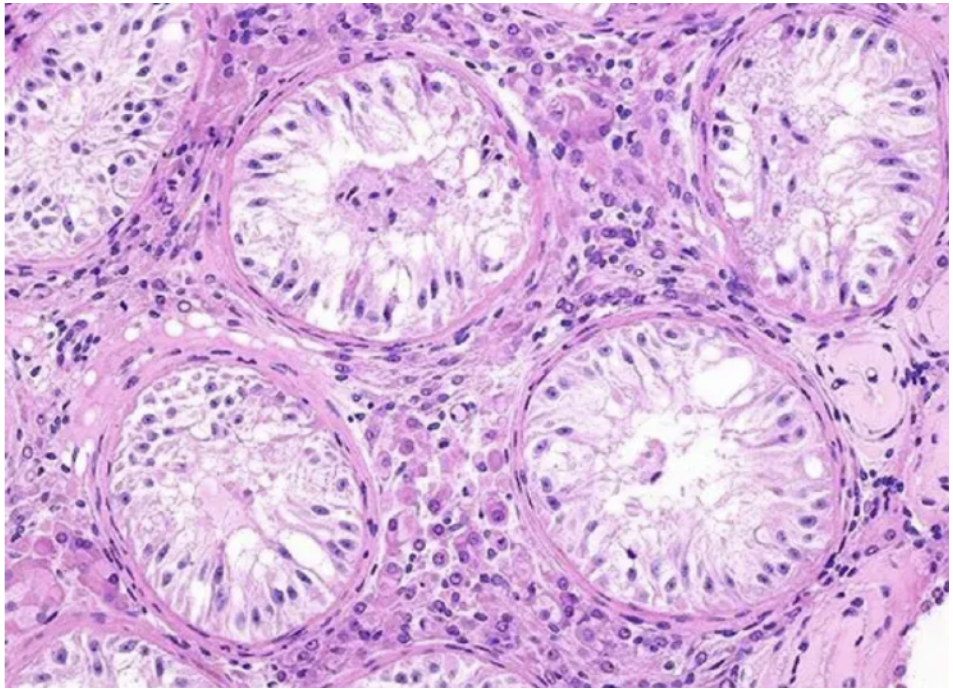

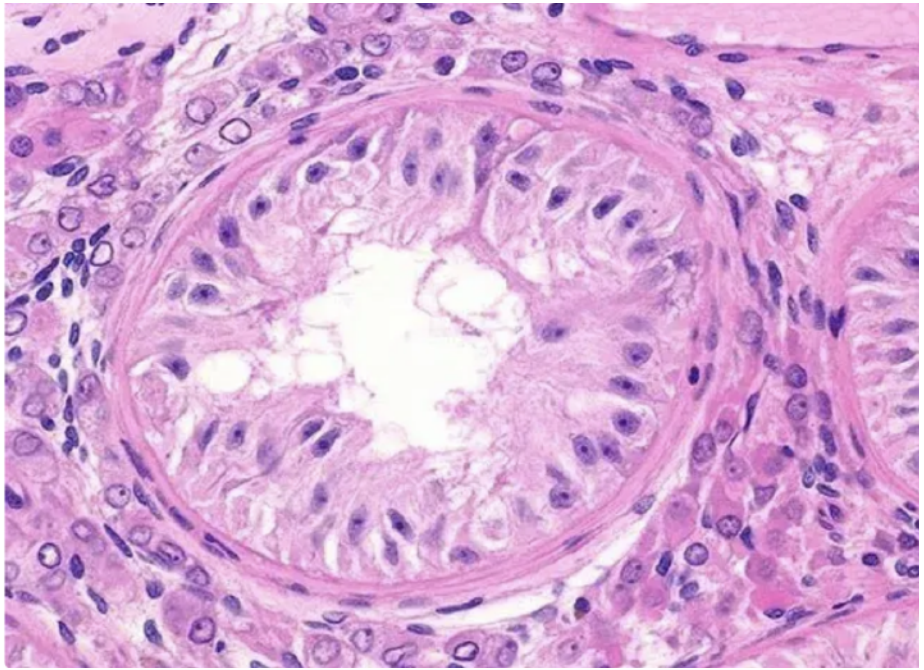

- The seminiferous tubules surrounded by thickened membranes and lined with a layer of mature Sertoli cell
- Rare islands of Leydig cells
- No germ cells

- Sertoli cells have oval nuclei.
- Leydig cells are normal in appearance but may appear to be increased in number.

Sperm Retrieval Techniques

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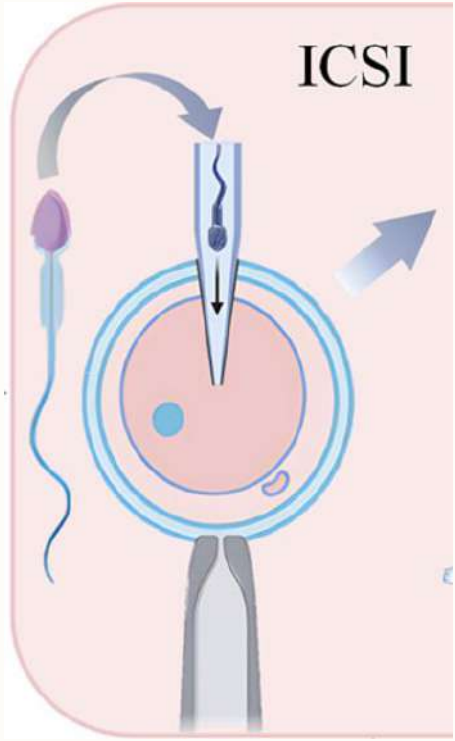
Testicular sperm extraction (TESE)

- Provides adequate tissue samples with a straightforward procedure
- It may cause testis damage due to excessive tissue removal

Microsurgical TESE

- Offers superior sperm retrieval rates and is less damaging than TESE
- Requires microsurgical expertise and resources



Majzoub, A., Viana, M. C., Achermann, A. P., Ferreira, I. T., Laursen, R. J., Humaidan, P., & Esteves, S. C. (2024). Non-obstructive azoospermia and intracytoplasmic sperm injection: unveiling the chances of success and possible consequences for offspring. Journal of clinical medicine, 13(16), 4939.

Sperm Retrieval Techniques

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	cTESE	mTESE
Surgical approach	Multiple blind random biopsies	Targeted microsurgical excision
Overall sperm retrival rate	35%	52%
Sperm retrieval rate in SCOS	13.3%	36.1%

Esteves, S. C. (2022). Microdissection TESE versus conventional TESE for men with nonobstructive azoospermia undergoing sperm retrieval. *International Braz J Urol*, *48*(3), 569–578.

Corona G et al.Sperm recovery and ICSI outcomes in men with non obstructive azoospermia: a systematic reviewandmeta-analysis. Hum Reprod Update 2019;25:733–757.

Sperm Retrieval Rates (SRR) by Etiologies

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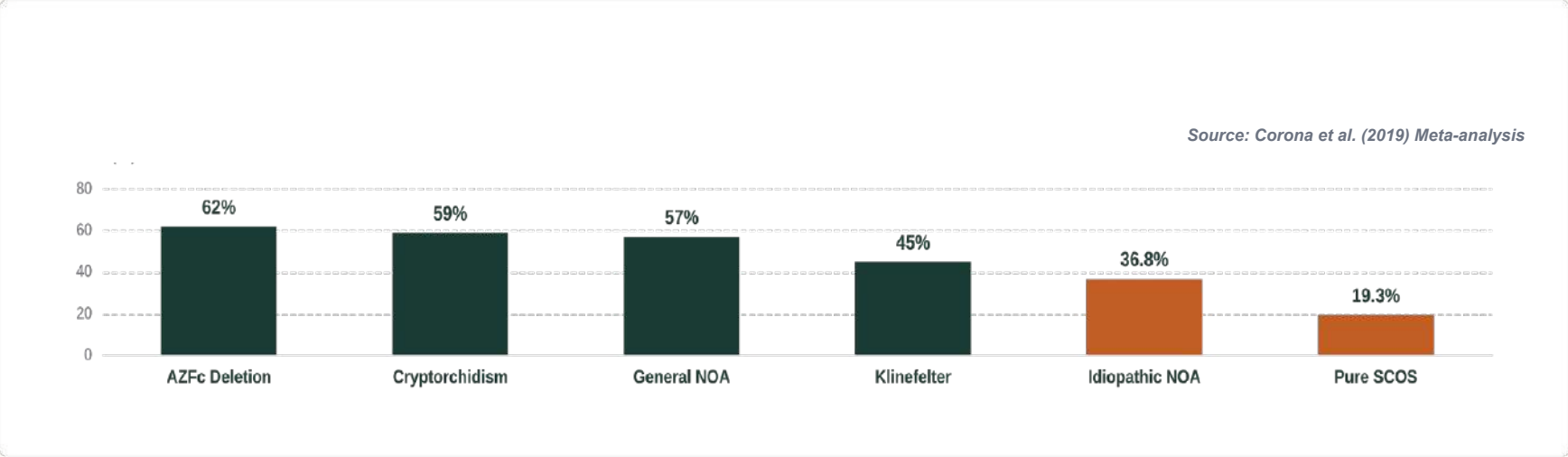

AZFc Advantage

AZFc microdeletions show high SRR (62%), making them favorable candidates for mTESE

Mosaic Potential

Secondary/Mosaic SCOS can reach up to 60% SRR with microdissection techniques

Genetic Prognostic Factors

Success rate is **nearly 0%** in:

- **AZFa Deletions**
- **AZFb Deletions**

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Medication therapy

- May enhance spermatogenesis in selected NOA patients, particularly in functional hypogonadism or low intratesticular testosterone.
  - hCG
  - FSH
  - Clomiphene citrate (SERM)
  - Aromatase inhibitors
- In pure Sertoli cell-only syndrome (SCOS), hormonal stimulation is largely ineffective due to absence of target germ cells.

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Thank you


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