



# ISSM Webinar Series

**Joint ISSM-JSM Webinar on “SEX & COVID-19: THE STATE OF THE SCIENCE”**



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## **SARS-CoV-2 Infection: Implications for the Male Reproductive System**

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## Disclosures (DJL)

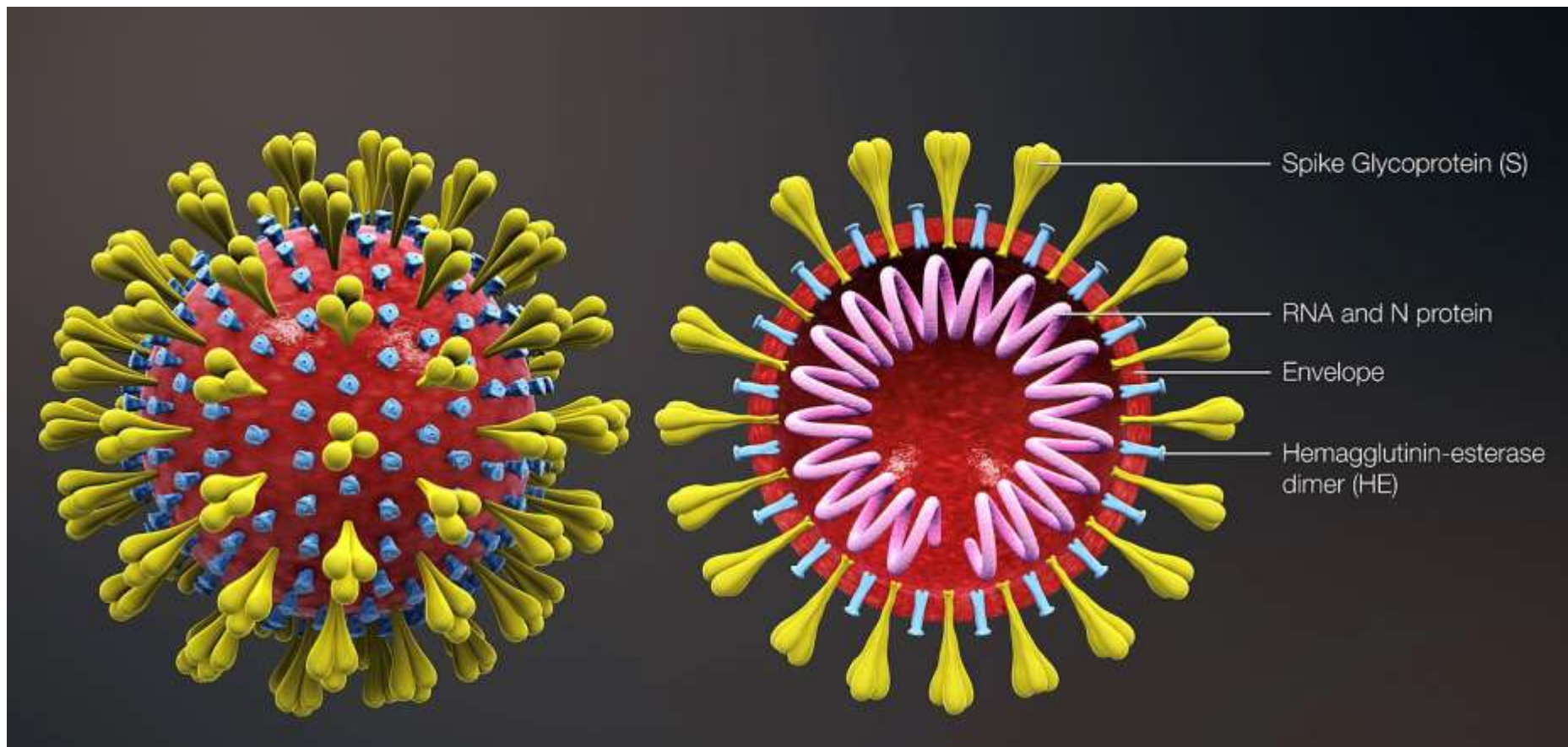
- Frederick J. and Theresa Dow Wallace Fund of the New York Community Trust
- World Health Organization (Editorial Board for WHO laboratory manual for the examination and processing of human semen Sixth edition)
- Celmatix Scientific Advisory Board (no financial compensation)

## Disclosures (NP)

- Frederick J. and Theresa Dow Wallace Fund of the New York Community Trust



# What is Known About SARS-CoV-2 Infection in Men?



# Impact of Gender: Men Are More Likely to Be Hospitalized and Die of Covid-19 than Women



## Total in NYC (N = 201,806)<sup>a</sup> as of June 3rd

	Male n=103,705	Female n=97,976	OR (95% CI)
Hospitalizations (n, %)	29,695 (28.6%)	22,743 (23.2%)	1.33 (1.30-1.35)*
Deaths (n, %)	10,239 (9.9%)	6,687 (6.8%)	1.50 (1.45-1.54)*

## All Deaths (N = 15,857)<sup>b</sup> as of May 16<sup>th</sup> (last date with data reported on associated conditions)

	Male n=9,634	Female n=6,223	OR (95% CI)
With known Underlying Disease (n, %)	7,563 (78.5%)	4,985 (80.1%)	0.91 (0.84-0.98)

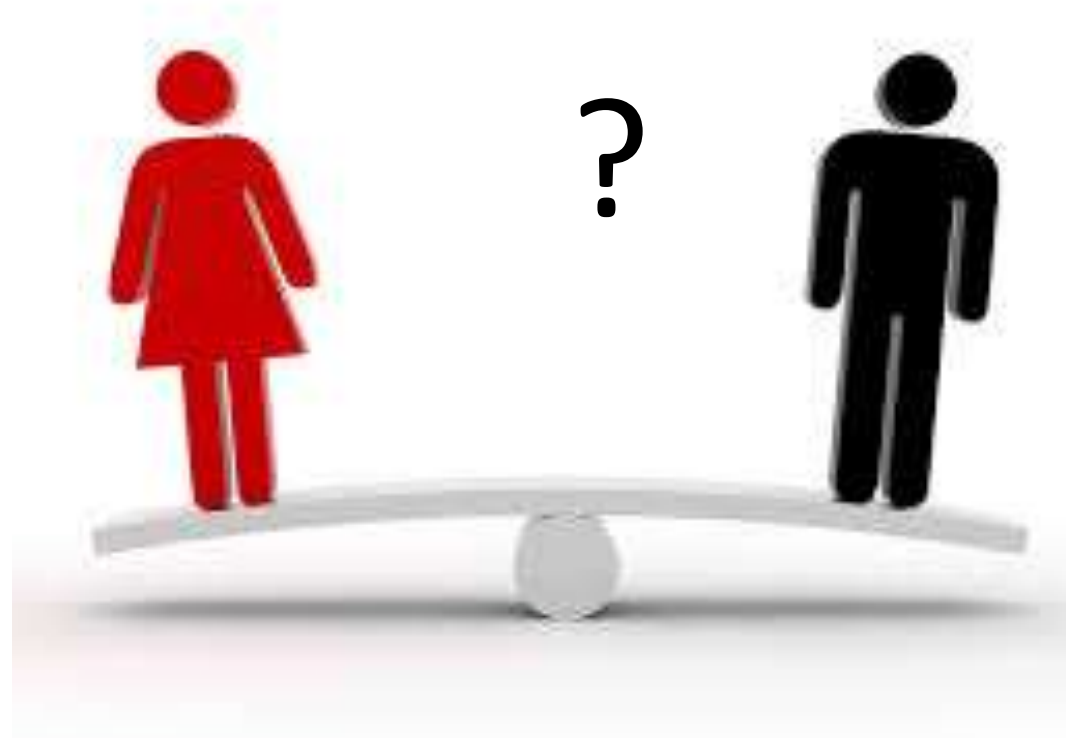
Unpublished. *In submission*



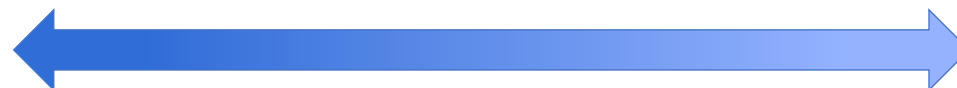
# Gender Differences Impact Disease Severity



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Biology



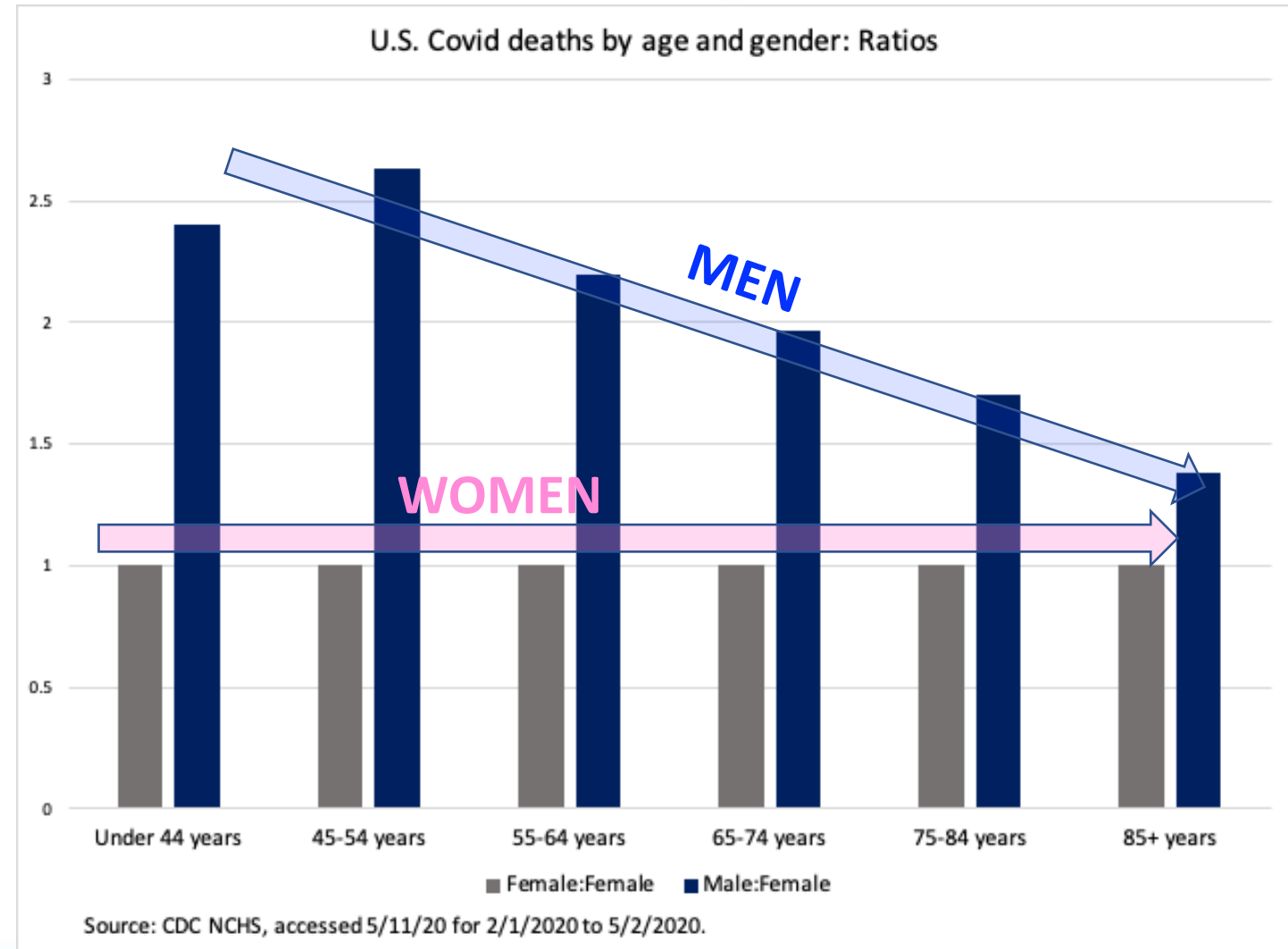
Lifestyle





# COVID-19 Deaths: Impact of Sex by Age

- **Men**, in general, are far more likely to die of Covid than **Women**
- Younger men have a higher death rate than older men
- The decline in the death rate by gender is reminiscent of the decline in testosterone levels in aging men



# Low or High T?



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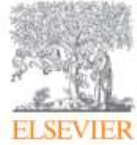


**Weill Cornell Medicine**  
Urology

<https://www.greatestphysiques.com/health/testosterone-levels-by-age/>



# Protective Effect of ADT?



Annals of  
Oncology  
Available online 6 May 2020  
In Press, Journal Pre-proof



Original Article

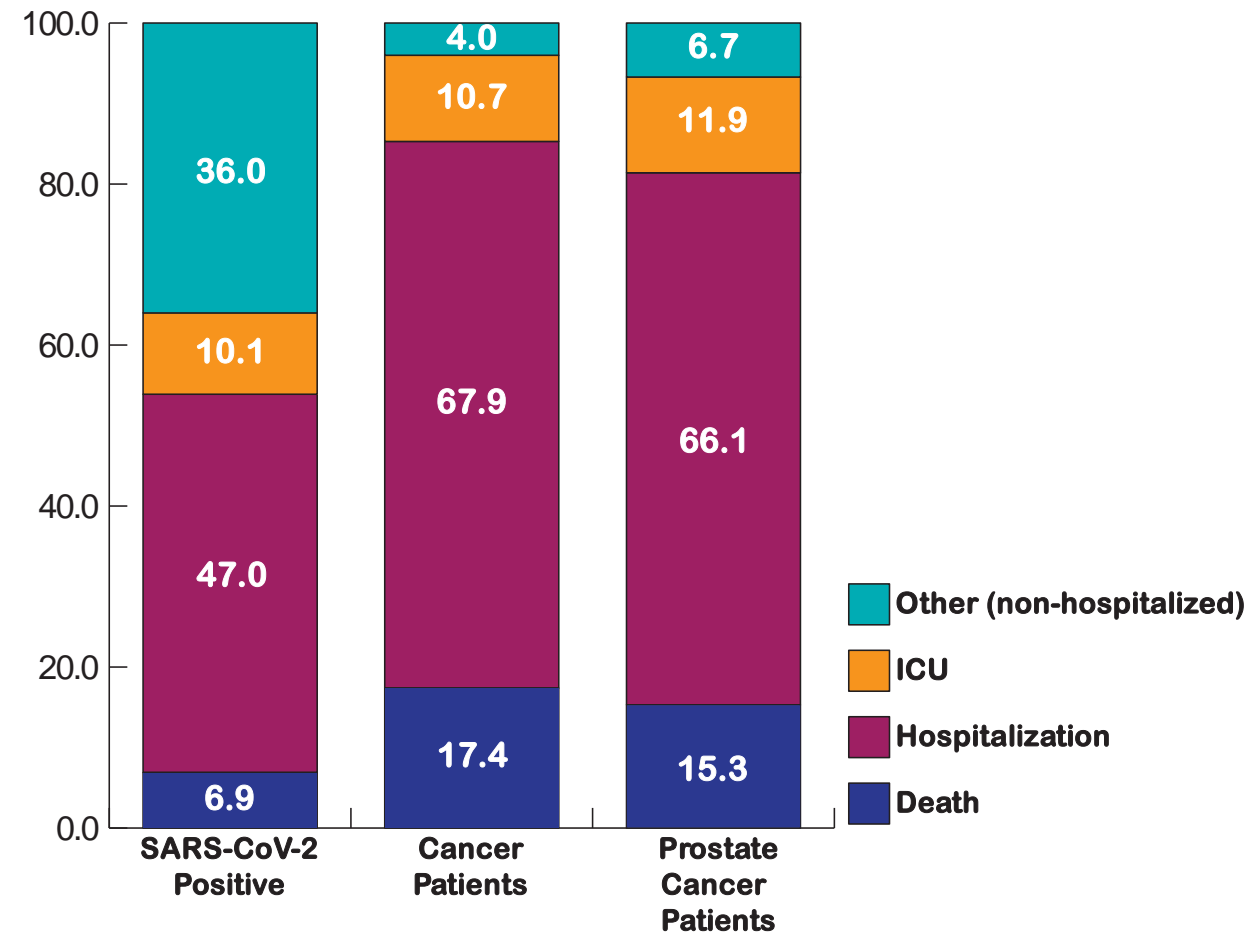
## Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (n=4532)

M. Montopoli<sup>1,2</sup>, S. Zumerle<sup>2,3</sup>, R. Vettor<sup>3</sup>, M. Rugge<sup>3,4</sup>, M. Zorzi<sup>4</sup>, C.V. Catapano<sup>5</sup>, G.M. Carbone<sup>5</sup>, A. Cavalli<sup>6</sup>, F. Pagano<sup>2</sup>, E. Ragazzi<sup>1</sup>, T. Prayer-Galetti<sup>7</sup>, A. Alimonti<sup>2,3,5,8</sup> ✉

- **Data suggest that cancer patients have an increased risk of SARS-CoV-2 infections compared with non-cancer patients.**
  - N=4532 men with laboratory confirmed SARS-CoV-2
  - A total of 68 hospitals were included
- **However, prostate cancer patients receiving ADT appear to be partially protected from SARS-CoV-2 infections.**



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# Ongoing Studies Focus on Endocrine Manipulation to Impact COVID-19 Disease Severity and Perhaps Androgen Regulation of Gene Expression



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- Androgen deprivation therapies
  - Anti-androgens
    - Bicalutamide
  - Degarelix
- Progesterone
- Estrogen
- Dexamethasone
  - Anti-inflammatory



# Circulating Testosterone and Androgen Receptor Transcriptional Activity Appear Correlated with COVID-19 Disease Severity



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- **Androgen receptor polymorphisms (CAG trinucleotide repeat length) that impact transcriptional activation by testosterone may impact COVID-19 disease severity in men**
  - **Supported by racial variations in CAG repeat length**
    - ~19 CAGs in African American, ~21 in Caucasian men, longest in Asian men ~25 CAG repeats
    - Men with shorter androgen receptor CAG repeats have increased androgen action as compared with men with longer CAG repeats
    - Men with shorter CAG repeats have increase disease severity then those with longer CAG repeats
- **Virilization as assessed by male pattern baldness (an androgen-mediated characteristic), androgenic alopecia, prostate cancer, androgen receptor CAG repeat length and COVID-19 disease severity ongoing studies appear consistent with this hypothesis**



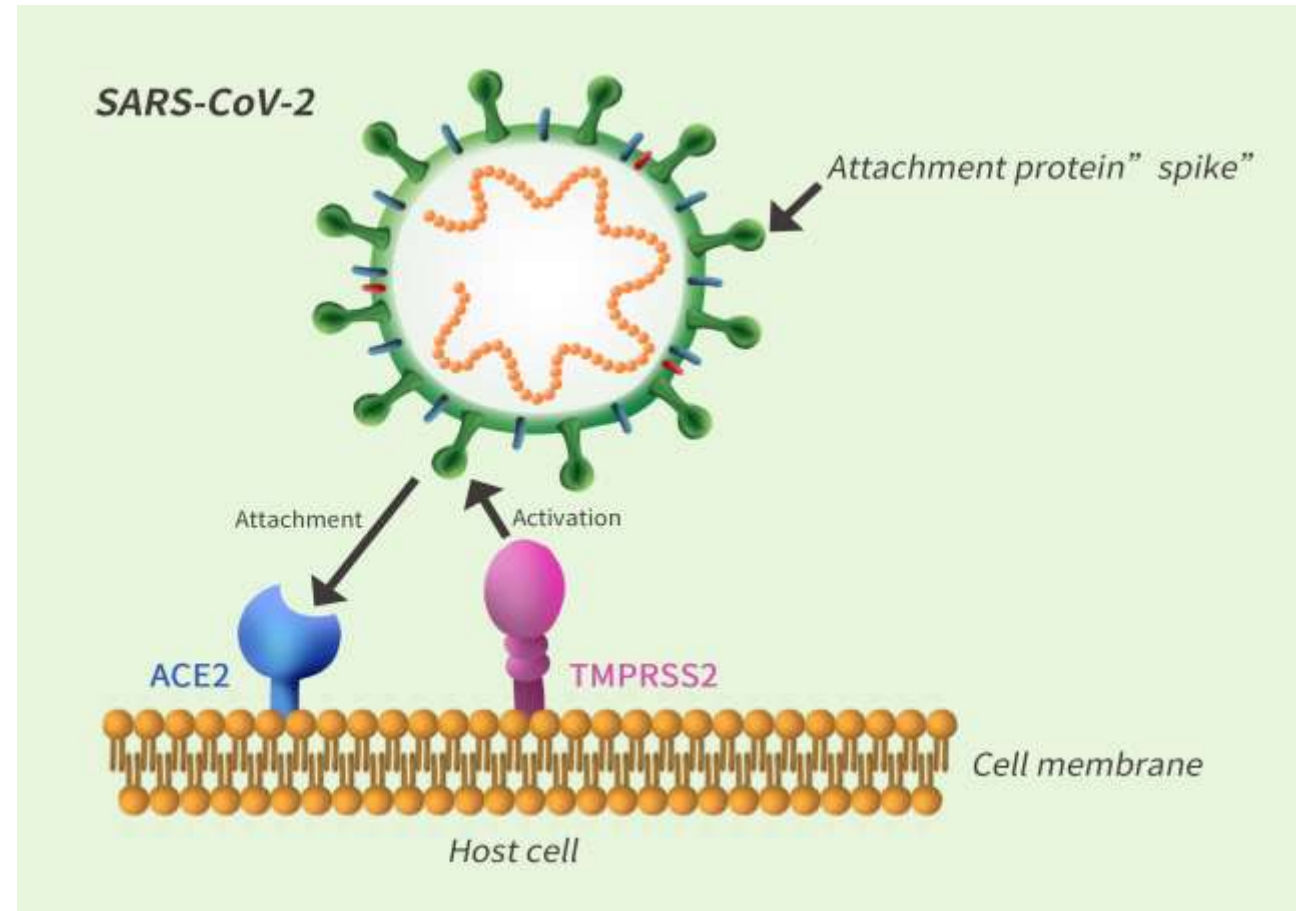
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Urology

# COVID-19 and ACE2/TMPRSS2



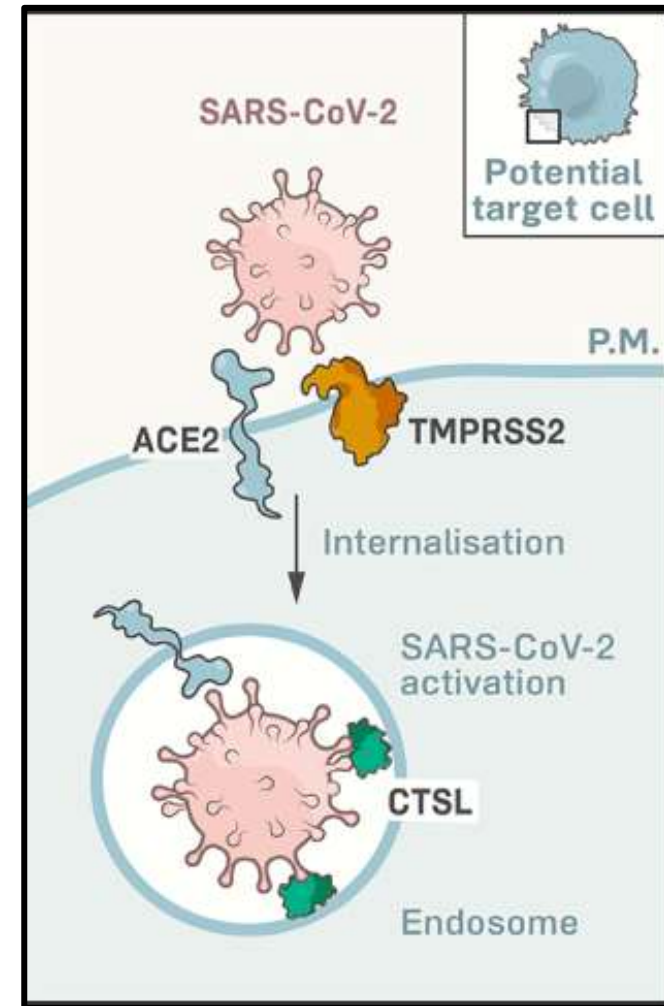
- In theory, organs with a high expression of the cellular receptor angiotensin converting enzyme 2 (*ACE2*), that allows SARS-CoV-2 to enter cells and/or transmembrane protease serine (*TMPRSS2*) are more vulnerable to infection.



# COVID-19 and ACE2/TMPRSS2 Expression in the Testis



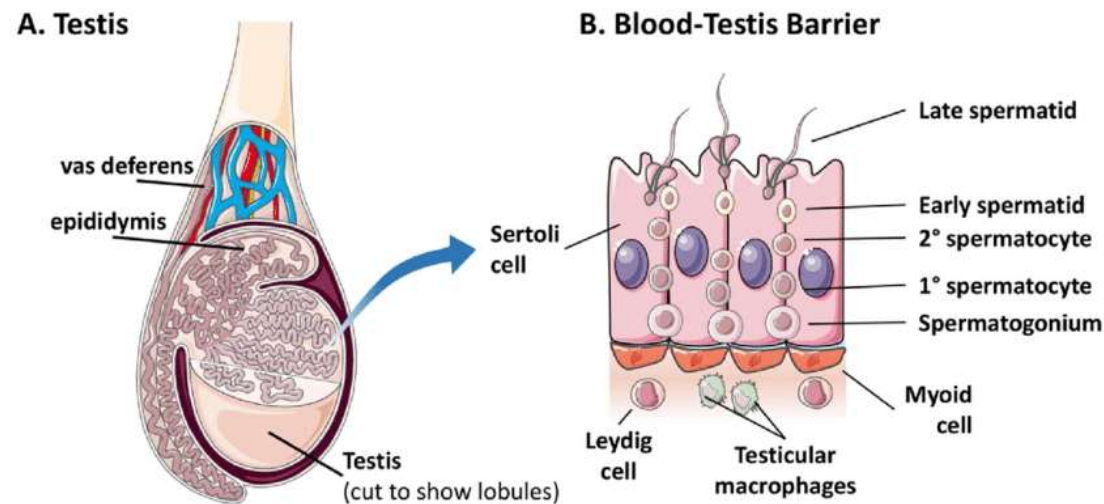
- In theory, organs with a high expression of the cellular receptor angiotensin converting enzyme 2 (*ACE2*), that allows SARS-CoV-2 to enter cells and/or transmembrane protease serine (*TMPRSS2*) are more vulnerable to infection.
  - ***ACE2***: Leydig cells, Sertoli Cells, Spermatogonia
  - ***TMPRESS2***: Spermatogonia and Spermatids



# Theories for Virus Affecting Testis? Orchitis is a Complication of SARS. Effect of SARS-Cov-2 on Testis is Unclear



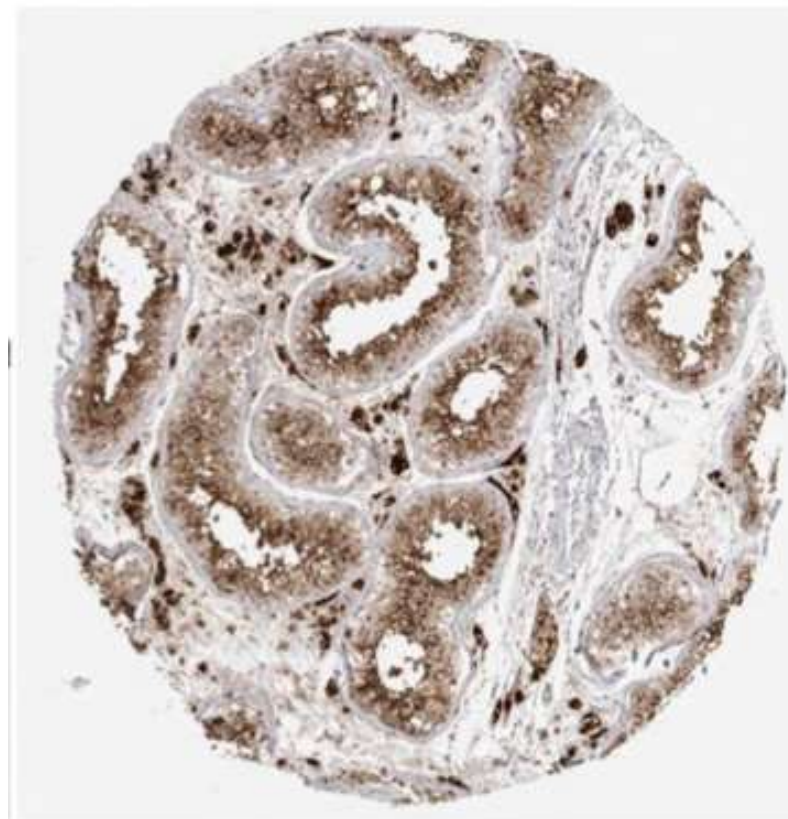
- Direct damage from virus resulting from inflammation
- Temperature effects on spermatogenesis
- Disruption to Sertoli cells which maintain the blood-testis barrier given ACE2 receptor presence



# Gender and Endocrine Aspects of SARS-CoV-2

- There is androgen-dependent tissue expression of both ACE2 and TMPRSS2 in androgen responsive tissues
- Innate difference in immune response in women vs men
- Different comorbidity profile
- Possible therapeutic approaches in male based upon disruption of androgen signaling

**ACE2** Is Highly Expressed in Testis



Testis

# Risk of viral sexual transmission via Semen?



	Pan et al. 2020 (F+S)	Li et al. 2020 (JAMA)	Nora et al. 2020 (F+S)	Song et al. 2020 (Medrxiv)
Location	Wuhan, Hubei	Shangqui, Henan	Duesseldorf, Germany	Wuhan, Hubei
Cases (state/province)	68,135	1,276 (91 in Shangqui)	37,395	68,135
Sample Size	34	38	34 (18 with disease)	13 (12 semen samples)
Disease Type	"milder" disease	Of the 6 positive: 4 "acute"; 2 "recovery"	14 mild 4 moderate	Mild/common: 11 Asymptomatic: 1
Detection in Semen?	0/34	6/38	0/18	0/12
Time Period	Median 31 (range 8-75)	Range 6-16 days	Range 8-54 days	?
Other findings	No ACE2/TMPRSS expression 6/34 scrotal discomfort	None	Semen parameter changes 1/34 with testicular discomfort (mod dx)	No RNA in testis tissue





# Should Sperm Cryopreservation Occur During the Pandemic?



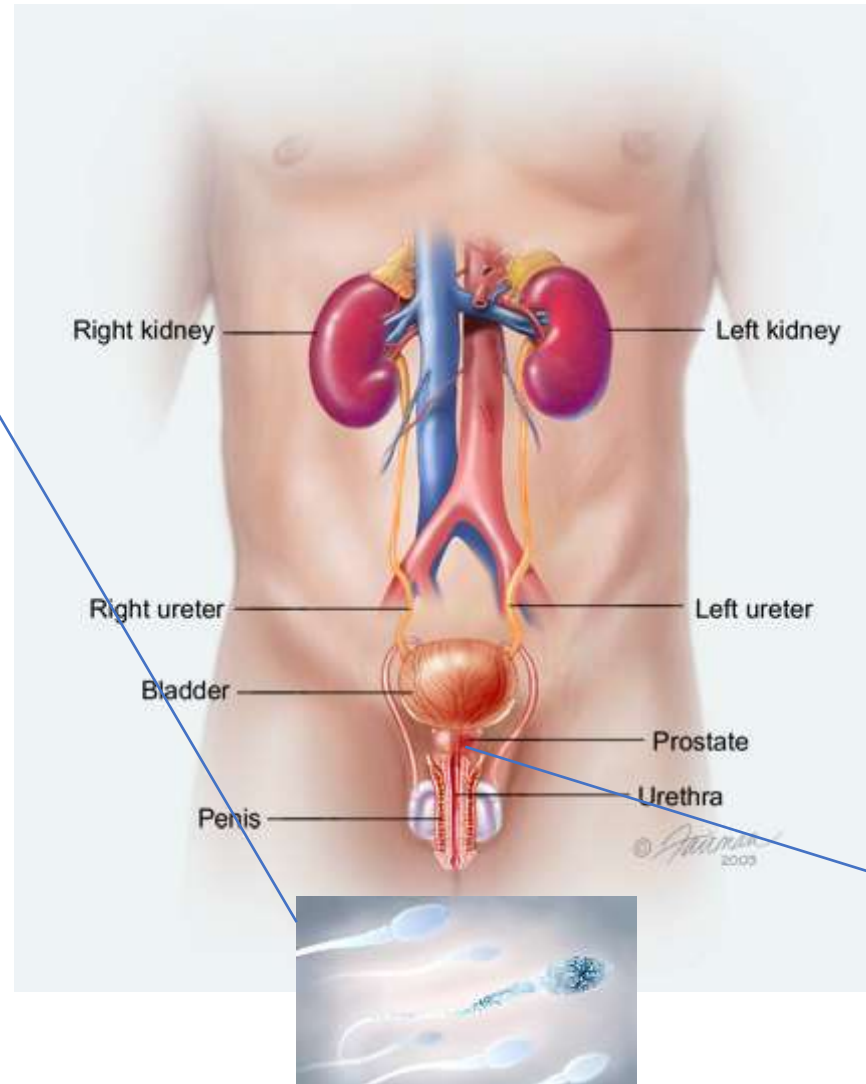
- **~27 viruses can be shed into the semen- sometimes long after symptoms abate**
  - Zika
- **SARS-CoV-2 viral shedding into semen observed thus far appears to be low**
  - Very low titres of SARS-CoV-2 have been detected in non-respiratory sites
- **Viruses are stable at ultra-low temperatures and SARS-CoV-2 may remain stable after cryopreservation and thawing**
- **Thus far, no recorded cases of viral cross contamination between cryopreserved semen samples**
  - Risk of cross contamination during storage thought to be negligible
- **Regardless, ideally samples processing should use secure and safe devices and cryovials should be segregated for storage**



# Men's Health Summary



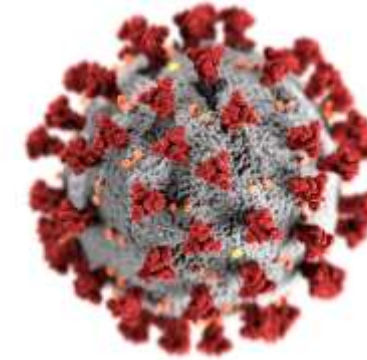
- **Semen Transmission**
  - Viral Detection: 6/172 patients (3.5%)
    - Shorter collection time and 4 of 6 had “acute” disease
- **Semen Quality**
  - Two reports showing impacts to sperm count and motility
- **Cryopreservation**
  - With utmost precautions and segregation of cryovials for storage



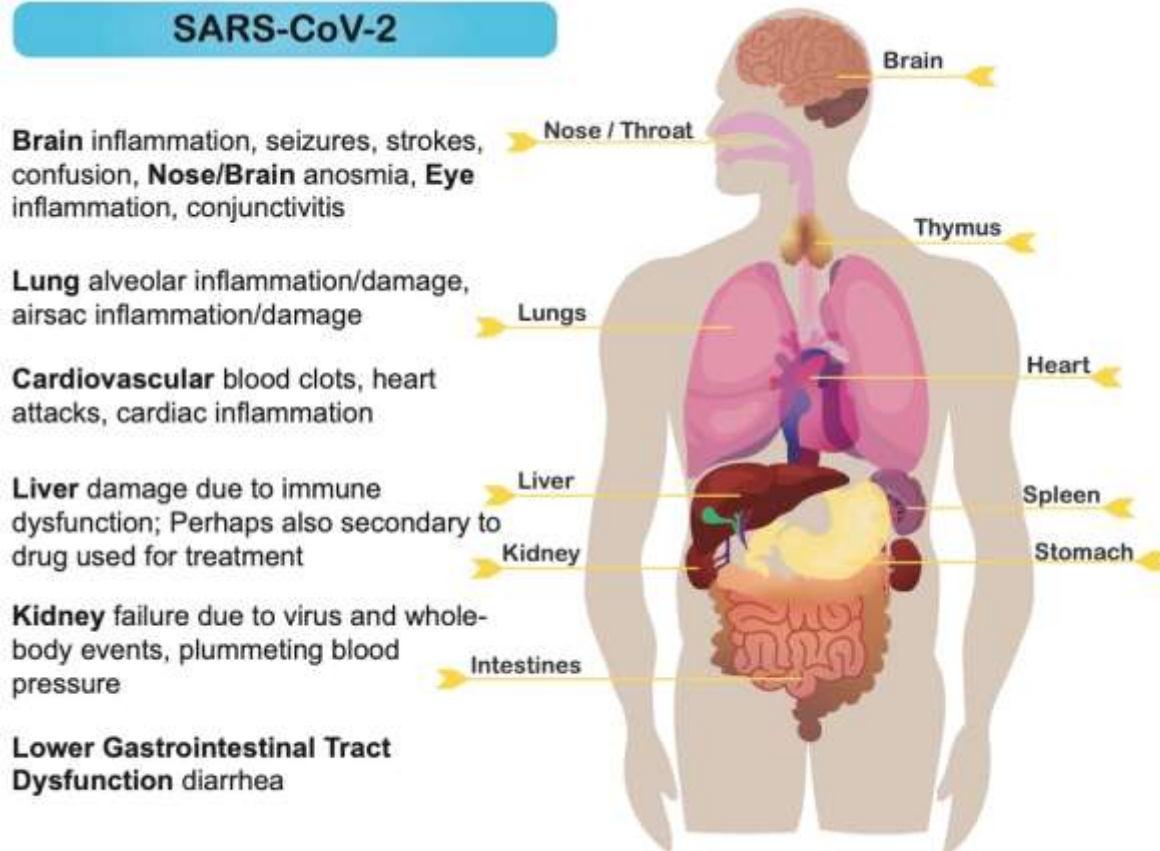
- **Virus in Testis**
  - No viral RNA detection
- **Orchitis**
  - 8 (9 with case report) total patients with scrotal discomfort
  - Limited physical exam findings
- **Prostate**
  - No evidence in EPS



# Although SARS-CoV-2 Infects the Lungs, Many Organs and Tissues Are Damaged in the More Severe Cases



## SARS-CoV-2



<https://www.sciencemag.org/news/2020/04/how-does-coronavirus-kill-clinicians-trace-ferocious-rampage-through-body-brain-toes>

- SARS-CoV-2 enters the body predominantly through the lungs
- In severe cases, a cytokine storm is elicited causing significant multi-organ damage. Direct systemic entry of the virus into cells expressing the ACE-2 receptor may occur.
- The effect of SARS-CoV-2 on the male reproductive track is only beginning to be discerned