

Community of Practice: COVID-19 Updates

Here's how Natera is helping you in the world of COVID-19

1st Edition: December 2020



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We understand that the transplant and nephrology communities are experiencing the complex effects of the Severe Acute Respiratory Syndrome 2 virus (SARS-CoV-2) on patient care. Natera has developed a quarterly newsletter to share our important findings as we navigate the ever-evolving pandemic.

Our goal is to be a trusted source to inform you on case studies, novel patient management strategies and commentary from your peers to optimize patient care together.

A Message from our Medical Directors at Natera, Inc

Dear Transplant & Nephrology Providers,

As we ride the waves of this pandemic, we recognize the value of a strong community of practice to provide assurance to our first-line workers, care teams and patients by learning from each other and incorporating the latest for continued safe, effective care.

The reality is that the COVID-19 pandemic has been particularly challenging for kidney transplant recipients (KTR) who are immunocompromised and as a result, highly anxious. A recent review examined the outcomes of 420 adult KTR with confirmed COVID-19.¹ The statistics in this study are concerning¹: 93% of the patients required hospitalization, 30% of whom required intensive care. Further, 44% had acute kidney injury (AKI) and 23% needed renal replacement therapy (RRT). In the study, 22% of these patients had died, and another 19% of patients were still in the hospital at the time of publication.

Even with patients who contracted the COVID-19 virus, the acute kidney injury (AKI) may result from a number of factors. An early study in non-transplant patients showed that the SARS-CoV-2 virus can directly infect kidney tissue and induce acute tubular damage.² Even renal damage due to an uncontrolled cytokine storm has been postulated.³ In the Marinaki et al review, 58% of patients had immunosuppression reduced or stopped, and therefore acute rejection must be considered as a cause of some of the cases of AKI.¹ Finally, a rapid-collapsing variant of focal segmental glomerulosclerosis (FSGS) has been described in both native and transplant kidneys in association with COVID-19, particularly in patients with apolipoprotein L-1 (APOL-1) risk alleles.⁴

Thus, there exists an unmet need to accurately and non-invasively surveil kidney transplant recipients for rejection when their immunosuppression is reduced or stopped.

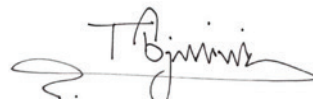
Natera's donor-derived cell-free DNA (dd-cfDNA) test, Prospera, is ideal for this. Additionally, Natera's new broad-based renal genetics panel, Renasisht, includes the APOL-1 risk gene, so you may identify patients at higher risk of nephropathy during a COVID infection.

Based on our experience of performing over two million cfDNA tests across women's health, oncology and organ transplantation, we continue to learn and optimize our own tests. As such, we want to share our ongoing learnings so we can together overcome the challenges to our discipline at this critical time.

Sincerely,



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Part of the Solution:

Two new kidney tests for COVID-19 patient care



The rundown:

- Prospera transplant assessment test allows for remote, non-invasive surveillance of rejection during times when COVID presents challenges for in-person visits
- Prospera’s unique enhancement flags elevated levels of background cell-free DNA common during a COVID infection to help avoid potential false negative results
- Renasight kidney genetics panel can identify the APOL1 genes in your COVID patients to understand any risk variants associated with collapsing glomerulopathy in patients^{1,2}

Remote, non-invasive assessment of transplant rejection during COVID times

Developed by Natera with our trusted legacy in cell-free DNA, Prospera is thoughtfully optimized to be a more precise, reliable tool for early, clinically meaningful rejection assessment.^{3,4,5}

Prospera’s high sensitivity of 89% and negative predictive value of 95% (at a 25% prevalence of rejection) means you can be confident when catching rejection during this critical illness, leading to possible treatment and/or resumption of immunosuppressants if consistent with the clinical picture.⁴ Further, Prospera has been reported to flag elevated background levels of cfDNA that may occur during a COVID infection as a way to avoid a false negative result.⁶



As such, Prospera can be integrated into your remote surveillance clinical workflow to more accurately catch rejection – even during the COVID-19 pandemic and infection.^{3,4}

Impact of APOL1 gene in COVID-19 patients

APOL1 high risk variants have been associated with collapsing glomerulopathy in patients with COVID.^{1,2} It has been posited that APOL1 requires a second hit to cause chronic kidney failure – including viral infections.⁸ As such, the SARS-CoV-2 virus may be providing the second hit in individuals with high risk APOL1 genotypes, leading to an increased incidence of nephropathy in these patients.^{1,2} Wu, et al., “found no direct viral infection in the kidneys, suggesting a possible alternative mechanism: a “two-hit” combination of genetic predisposition and cytokine-mediated host response to SARS-CoV-2 infection.”²

Further, the gene has been implicated in some disparities currently related to the morbidity and mortality associated with the COVID-19 pandemic, specifically in Americans of African descent. African Americans have a higher incidence of the APOL1 risk variant than other ethnic backgrounds.⁹



Understanding an individual’s APOL1 status, using a test like Renasight, may help better understand potential risks related to COVID-19 infections.

References:

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- 8 Huijuan Wu, Christopher P. Larsen, Cesar F. Hernandez-Arroyo, Muner M.B. Mohamed, Tiffany Caza, Moh'd Sharshir, Asim Chughtai, Liping Xie, Juan M. Gimenez, Tyler A. Sandow, Mark A. Lusco, Haichun Yang, Ellen Acheampong, Ivy A. Rosales, Robert B. Cotvin, Agnes B. Fogo, Juan Carlos Q. Velez. *JASN* Aug 2020, 31 (8) 1688-1695; DOI: 10.1681/ASN.2020050558
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Featured Case Study:

Transplant assessment in the age of COVID-19

Transplant patients are at an increased risk of severe COVID-19 infection due to immunosuppression and other comorbidities. Surveillance with dd-cfDNA provides a non-invasive option and may alert to an issue with an allograft, triggering prompt investigation. There is mounting evidence that background cfDNA levels become elevated during infection.¹⁻³

Patient History:

- 60 year old, black female with cerebral palsy in a long term care facility**
- Experienced end-stage renal disease, secondary to hypertension**
- Received a deceased donor kidney transplant**
- Received envarsus and myfortic**



The Journey:



- 8.6 months post-transplant, patient contracted a fever and sent to the local emergency department, where she was diagnosed with COVID-19
- Otherwise clinically stable so stayed in the COVID ward within the long term care facility



- 15 days later, she returned to the hospital with mildly elevated creatinine
- **Prospera test showed a result of 0.12% dd-cfDNA with high background cfDNA levels of 18.1x the median**



- Myfortic was halted but continued on prednisone
- Discharged seven days later with normal renal function



- **60 days later, a subsequent Prospera test revealed a 0.43% dd-cfDNA result with background cfDNA levels of 1.1x the median**

Key Takeaway: COVID-19 may cause very elevated levels of background cfDNA. Therefore patients are at-risk for false negative interpretation, which is especially concerning with immunosuppression reduced in response to the infection. Prospera proactively alerts the physician if a result may yield a false negative in a high-risk patient.

Exploratory Questions:

- Do you have patients with COVID-19 who might benefit from Prospera?
- How have you managed immunosuppressive therapies in your kidney transplant patients who have COVID-19?
- What might you do differently after reading this case study?

References:

1 Ahmed A, et al (2016). Clin Lab., 62(12):2395-2404
 2 Natera data on file, 2020
 3 Bunnapradist, S., Schaenman, J., Lum, E.L., Gauthier, P.M., Ahmed, E., Billings, P.R. (2020, October). Case study: Kidney transplant patient with COVID-19: Impact of viral infection on background cell-free DNA in a donor-derived cell-free DNA rejection assay. Poster presented at American Association of Nephrology Kidney Week 2020. <https://www.asn-online.org/education/kidneyweek/>

Featured Case Study:

Linking acute kidney injury severity in COVID-19 to the APOL1 Gene


Based on real Renasight cases

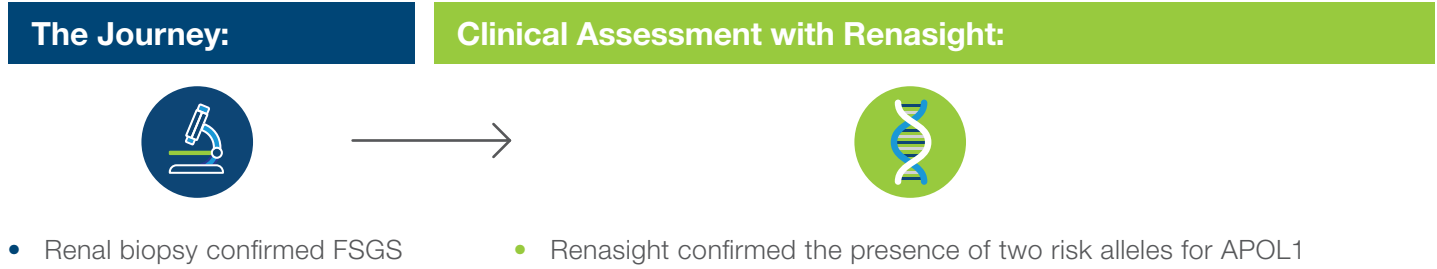
Having two risk alleles for APOL1 are associated with FSGS in patients who are critically ill due to COVID.

Patient History:

64 year old female hospice patient

Acute kidney disease with an atrophic kidney





Key Takeaway: Patients who have two risk alleles for APOL1 kidney disease as a result of COVID.

Exploratory Questions:

- What do you think the link is between APOL1 gene to COVID-19?
- Are patients indeed at a higher risk to develop COVID-19-related nephropathy with the two risk alleles?
- Have you seen any patients with the APOL1 gene develop COVID-19 related nephropathy?

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 1 Velez, J.C.Q., Caza, T. & Larsen, C.P. COVAN is the new HIVAN: the re-emergence of collapsing glomerulopathy with COVID-19. Nat Rev Nephrol 16, 565–567 (2020). <https://doi.org/10.1038/s41581-020-0332-3>
 2 Noble R, Tan M, Y, McCulloch T, Shantier M, Byrne C, Hall M, Jesky M: Collapsing Glomerulopathy Affecting Native and Transplant Kidneys in Individuals with COVID-19. Nephron 2020. doi: 10.1159/000509938

A Call for Stories:

Share your learnings with our community



Natera wants to thank all the healthcare professionals who have been on the frontlines of this crisis. Your dedication, determination, grit, resilience and sacrifice over the last few months have been inspiring and invaluable to our community.

We extend our call for stories, research and experiences to our transplant and nephrology partners so we can continue to learn together and improve patients lives during these uncertain times.

Please contact Prospera@natera.com to discuss with the Natera Clinical Team.

Visit natera.com/covidCOP to see what else our community is sharing.