CareDx, Inc. (CDNA)

Pivotal Kidney Transplant Test Headed for Rejection

We are short shares of CareDx, a $1.7bn diagnostics company whose share price has increased by 30x over just the last two years and now trades at over 18x sales. The meteoric rise and generous valuation have come in the wake of excitement over the commercialization of AlloSure, a blood test intended to identify organ rejection in kidney transplant recipients. Transplant nephrologists have long used measures of kidney function to assess the probability of rejection, with a tissue biopsy providing a definitive diagnosis. To hear CareDx tell it, AlloSure is the long sought-after silver bullet for rejection diagnosis, with the potential to "revolutionize the treatment of kidney transplant patients." It can help physicians "detect rejection of a donated organ ***earlier and more accurately***" than traditional blood-based measures of kidney function and "***reduce the use of invasive biopsies***." [emphasis added]

But alas, as hard as CareDx has tried to finesse the numbers into telling a good story, it's difficult to escape the simple fact that AlloSure is mostly useless, and potentially dangerous if used improperly. It should be obvious that a diagnostic test for transplant rejection that misses about 40% of rejections compared to the current standard of care has little place in clinical practice. But the stars have fortuitously aligned for CareDx: under the financial cover of broad (but *provisional*) Medicare coverage, the company has enlisted dozens of influential transplant researchers in the country's largest clinics to conduct numerous large-scale studies evaluating AlloSure. The hope is to conclusively proclaim its status as a diagnostic panacea.

The data coming out of those studies, though, is exceptionally poor, even as AlloSure revenues are overwhelmingly comprised of *utilization in those studies*. That leaves CareDx in a precarious position, particularly as physicians wise up to the futility of AlloSure. We calculate that CareDx has faced a *quarterly* attrition rate on AlloSure's surveillance patient population of 20-30%. That's staggering for a diagnostic test with a captive patient population, particularly one that's paid for almost entirely by Medicare. It's perhaps less surprising when viewed in the context of the continuous trickle of papers and data revealing AlloSure's futility in identifying the most common types of kidney rejection.

That data will present an even bigger obstacle for CareDx when Medicare reconsiders its coverage parameters, which are *conditional on the results of a large clinical trial under way*. It's already clear, in our view, that AlloSure won't be able to serve as a diagnostic tool in the way it was originally envisioned, which would jeopardize Medicare coverage. It's therefore unsurprising to see that, in an attempt to stay relevant, recent AlloSure research sponsored by CareDx has been pivoting hard, aiming to prove AlloSure's worth in a subset of the overall kidney transplant market. The problem, as we shall see, is that the subset being targeted is a fraction of the $2 billion that CareDx has declared its addressable market.

To make matters worse, several competing rejection diagnostic tests are slated to hit the market in the next few months, fresh off their own provisional Medicare coverage approvals. Some have similar mechanisms of action as AlloSure but promise to be more accurate and potentially cheaper. Others have novel mechanisms based on genomic markers and are backed by impressive clinical evidence. They will now get the chance to vie for their own place in clinical studies, and we expect them to hasten the unraveling of AlloSure that's already under way. CareDx, reliant on a single ineffective test, will soon confront its own terminal diagnosis.

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I. Investment Highlights

AlloSure is ineffective in identifying kidney rejection. The gold standard of kidney rejection diagnosis for transplant recipients is a biopsy. Kidney transplant recipients are subject to ongoing monitoring post-transplant, during which they undergo routine screening to assess kidney function. Abnormal serum creatinine or, less frequently, high urine protein levels are typically the first sign(s) of decreased kidney function. If they lead to suspicion of rejection, a biopsy is performed and examined in order to determine whether the kidney is suffering from rejection.

But creatinine is an admittedly flawed marker:

- False Positive Rate. Creatinine levels are an indicator of kidney function, and rejection is just one of several reasons they may be elevated. As a marker of kidney rejection, the false positive rate is high, as only about a third of biopsies that are performed due to elevated creatinine are diagnosed as rejection.
- False Negative Rate. Rejection can occur with no short-term loss of kidney function, and creatinine measurements are incapable of picking up rejection in such cases. This phenomenon, called "subclinical" rejection, is estimated to occur in 15-35% of transplant recipients that have normal creatinine measurements.

The field of nephrology has long pursued a noninvasive biomarker of kidney rejection that would a) eliminate the false positive problem, thereby reducing unnecessary biopsies and b) detect subclinical kidney rejection. AlloSure – the diagnostic test responsible for most of CareDx's market capitalization – is the first attempt (but certainly not the last) to commercialize such a biomarker. In CareDx's telling, AlloSure provides "precise, actionable results" and is "more accurate than serum creatinine in diagnosis of active rejection." It also provides a "sensitive, accurate, and precise measure of organ health." We believe that the underlying message – that AlloSure is a precise method that can be used to establish the presence or absence of kidney rejection – *couldn't be further from the truth*.

Every single clinical paper and study of AlloSure leads, in our view, to one inescapable conclusion: **AlloSure is an utter failure as a comprehensive biomarker of rejection**. In fact, based on the flagship paper[1] used by CareDx to demonstrate the test's clinical utility, doctors using AlloSure to rule out rejection, as per the company's marketing materials, *would miss about 40% of rejection episodes that would otherwise be detected using the current standard of care*. In the course of our diligence we found that in some clinics doctors have begun using AlloSure to diagnose rejection, and we believe this puts a significant number of kidney transplant recipients at unnecessary risk. Abnormal creatinine levels may *over*diagnose

[1] Bloom RD., Bromberg JS, Poggio ED, et al. Cell-Free DNA and Active Rejection in Kidney Allografts. *J Am Soc Nephrol* 2017; 28:2221

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rejection (high false positive rate), but AlloSure presents the much more severe problem of *under*diagnosing rejection (high false negative rate).[2]

What about subclinical rejection, which goes undetected by creatinine measurement? In CareDx's DART clinical trial, only 3.9% of a reference cohort of patients who exhibited no signs of impaired kidney function tested positive for kidney rejection using AlloSure.[3] But studies documenting the results of surveillance biopsies reveal that the subclinical rejection rate *ranges from 15-35%*. **In other words, AlloSure misses the overwhelming majority of subclinical rejection episodes**, and that's ignoring the false positives in that 3.9% number.

More recent studies confirm the problems with AlloSure implicit in the DART trial and cast further doubt on the accuracy of the test, strongly suggesting that AlloSure is structurally incapable of identifying T-Cell-Mediated Rejection (TCMR), by far the most common type of acute rejection. The consistent weakness of AlloSure across multiple studies is that, in statistical parlance, its *sensitivity* – the probability that the test result will be positive given the occurrence of rejection – is so low as to make the results unreliable at best, and dangerous if misused.

AlloSure's commercial success is unsustainably built on collapsing clinical-study usage and conditional Medicare coverage. If AlloSure is such a poor biomarker, how did it reach a ~$45 million annual revenue run rate in less than 18 months? As a Laboratory Developed Test (LDT), the only barrier to commercialization was payor coverage, and over 90% of kidney transplant procedures qualify for Medicare coverage, which includes all medical care for 3 years post-transplant. So the only third party payor that really matters for AlloSure (for now) is Medicare, which is fortunate because LDTs can obtain broad Medicare coverage just by competently navigating the MolDX program.

MolDX, short for Molecular Diagnostic Services, is a program run by Palmetto GBA, a Medicare Administrative Contractor (MAC) in the Southeast, and set up in 2011 in order to manage the growing number of genetic and molecular diagnostic LDTs. Most of the MACs have outsourced their LDT coverage decisions to MolDX, so the program is effectively a gateway to national coverage and reimbursement for any LDT. To get a Local Coverage Determination (LCD) from MolDX, a test must pass a technical assessment, which involves subject matter experts determining whether it has demonstrated "analytical validity, clinical validity, and clinical utility."

MolDX will normally grant an LCD even with limited evidence of clinical utility, conditional upon further research that is expected to *prove* clinical utility. The LCD for AlloSure states that MolDX "recognizes that the evidence of clinical utility for the use of AlloSure in its intended use population *is promising at the current time*. However, this contractor believes that forthcoming

[2] CareDx can technically claim that AlloSure is "more accurate" than serum creatinine measurement because it has a lower rate of false positives. But *accuracy* is not the goal of rejection testing, rather, *detecting rejection* is.
[3] Bromberg JS, Brennan DC, Poggio E, et al. Biological Variation of Donor-Derived Cell-Free DNA in Renal Transplant Recipients: Clinical Implications. *J Appl Lab Med* 2017; 2:309

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prospective clinical studies will demonstrate improved patient outcomes. *Continued coverage for AlloSure testing is dependent on annual review by this contractor of such data and publications*." [emphasis added] For now, though, AlloSure is covered and reimbursable for any kidney transplant recipient covered by Medicare.

That LCD went into effect on October 2, 2017, which partly explains the AlloSure revenue ramp that started in the fourth quarter of 2017. But it's also worth putting AlloSure into the more general context of organ rejection research. The transplant community has always dreamed of a noninvasive "silver bullet" to detect organ rejection, and the genomic revolution has brought with it hope that such a test could be developed. AlloSure measures the quantity of donor-derived cell-free DNA (dd-cfDNA) in the patient's blood stream, and the hypothesis that cfDNA might signal organ rejection was first advanced as far back as 1998. Research on the matter started gaining momentum in 2011 and, since then, small studies of cfDNA as a rejection marker in heart, lung, and kidney transplants showed promise but were inconclusive. Even the March 2017 flagship paper that arose out of CareDx's DART study was small (102 patients, only 27 of whom were diagnosed with rejection) and while "promising" (in the words of MolDX), it was far from conclusive.

The LCD from MolDX in late 2017 essentially subsidized further studies of cfDNA by providing reimbursement for AlloSure, which flung open the door for large-scale studies to take place. cfDNA, which had been the subject of intense speculation and curiosity for a decade, could now be studied as a noninvasive rejection biomarker in large numbers and at negligible cost. On top of the latent demand for studying cfDNA, CareDx shrewdly provided financial support and funding to renowned transplant nephrologists in over two dozen of the largest clinics nationwide, ensuring a steady stream of multi-year studies that would provide "recurring" demand for AlloSure tests. The company also immediately began enrollment on a massive 1000-patient clinical trial (KOAR), which, in the company's own words, would "include approximately 10,000 reimbursed AlloSure tests over the next 3 years, thus representing incremental AlloSure volume as well as another revenue driver going forward."[4]

As with the routine screening of transplant recipients (see below), AlloSure usage is being studied on a protocol basis, with CareDx routinely disclosing on earnings calls the number of patients on an AlloSure surveillance protocol. Recently, the company has disclosed a quarterly attrition rate of 10% for these surveillance patients. While that still implies an incredible 35% annual drop-out rate, *we believe that the real attrition rate is much higher*. Given the historical disclosure of quarterly surveillance patients, and recent disclosures regarding the total number of patients who have *ever* been provided AlloSure results, we calculate an attrition rate for surveillance patients of approximately *20-30% per quarter, or a staggering 70% annually*. Consider that CareDx has provided results to "over 8,000 patients" in the span of 6 quarters, and yet only about 3600 patients are currently on an AlloSure surveillance protocol.

[4] 11/9/2017 – CareDx Fiscal 2017 Third Quarter Earnings Call

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The disclosures also suggest that over 90% of AlloSure revenue comes from these surveillance patients. Ironically, AlloSure's revenue comes almost entirely from transplant clinics studying it as a routine screening tool, but finding it so inadequate that they rapidly drop it. We expect the patient recruitment treadmill will soon become impossible to outrun.

National Kidney Foundation Routine Screening Guidelines for Clinicians

ROUTINE SCREENING AFTER KIDNEY TRANSPLANTATION

Screening Test	Screening Intervals by Time After Transplantation					
	1 week	1 month	2-3 months	4-6 months	7-12 months	>12 months
Creatinine[a]	Daily	2-3 per week	Weekly	Every 2 weeks	Monthly	Every 2-3 months
Urine protein[b]	Once		Every 3 months			Annually
Complete blood count[c]	Daily	2-3 per week	Weekly	Monthly		Annually
Diabetes[d]	Weekly		Every 3 months			Annually
Lipid profile[e]	–	–	Once	–	–	Annually
Tobacco use[f]	Prior to discharge		–	–	–	Annually
BKV NAT[g]	Monthly			Every 3 months		–
EBV NAT (seronegative)[h]	Once	Monthly		Every 3 months		–
Blood pressure, pulse, height, body weight	Each clinical visit					

BKV, BK polyoma virus; EBV, Epstein-Barr virus; NAT, nucleic acid testing.
[a]Serum creatinine. Suggest estimating GFR whenever serum creatinine is measured [R 8.3.1 (2D)] using one of several formulas validated for adults (2C), or the Schwartz formula for children and adolescents (2C).
[b]Urine total protein and/or urine albumin.
[c]Complete blood count, including white blood count, hemoglobin and platelet counts.
[d]Screen for diabetes with fasting blood glucose, glucose tolerance test, or HbA_{1c} level.
[e]Lipid profile includes fasting cholesterol, LDL-C, HDL-C, and triglycerides.
[f]Screen for tobacco use.
[g]Screen for BKV using plasma NAT.
[h]Screen for EBV using plasma NAT in patients with no antibody to EBV at transplant.

Source: National Kidney Foundation: Managing Kidney Transplant Recipients

Poor clinical results leave CareDx open to significant regulatory and competitive risks. In addition to massive patient attrition, CareDx faces the risk of Medicare scaling back coverage. For AlloSure to secure broad permanent MolDX coverage, it will need to show that it can "[identify] renal transplant recipients who may use AlloSure testing in the first year post transplant to safely avoid unnecessary procedures and/or interventions." In other words, it needs to obviate a biopsy by conclusively ruling out rejection in transplant patients. As mentioned above and detailed below, the data unambiguously show that's implausible. But in patients with biopsy-diagnosed antibody-mediated rejection (ABMR) – a small subset of total transplant recipients – AlloSure *might* effectively monitor the progress of treatment over time. That's a very niche market compared to CareDx's preferred regiment of testing all transplant recipients several times annually for years. CareDx sizes its market at $2 billion, while the ABMR-monitoring market size is closer to ~$100 million. We expect that after evaluation of the KOAR data (in 2022), Medicare coverage will thus be significantly scaled back.

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At the same time, the same structural processes that helped AlloSure (at least temporarily) are allowing competitors to validate other diagnostic rejection tests, and at least two have already received a preliminary LCD from MolDX granting Medicare coverage. One of these is a dd-cfDNA test from Natera, a company that has a long history of using cfDNA in prenatal applications. We are skeptical about the ability of cfDNA to significantly impact kidney transplant diagnostics, but Natera may be able to measure cfDNA more accurately, and has a cost structure low enough to significantly undercut AlloSure on price. There are also other cfDNA assays that could be commercialized rapidly, as well as new genomic tests that are aimed at precision diagnosis of specific kinds of organ rejection.

CareDx scored reimbursement support for a test whose mechanism of action has been a curiosity for decades. But commercialization is a double edged sword: the rigorous testing it has catalyzed is coming up empty, driving rapid patient attrition and putting the company at risk of both losing Medicare coverage and being run over by competition.

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II. Company Overview

CareDx: Capitalization and Financial Results

Capitalization

Share price ($)	$ 37.40
Fully diluted shares (mm):	
Shares outstanding	41.9
Dilutive impact of options/RSUs	3.1
Total	45.0
Fully diluted market cap (mm)	$ 1,685
Less: cash	57
Enterprise value	$ 1,627
EV/revenue (trailing)	18.4x

Financial Results

	2016	2017	2018	TTM
Revenue	$ 41	$ 48	$ 77	$ 88
EBITDA	(13)	(13)	(10)	(11)
EBITDA Margin	*-31%*	*-27%*	*-13%*	*-12%*
AlloSure Rev. (est)	$ -	$ 0.4	$ 21.1	$ 30.9

Source: company filings, Kerrisdale analysis

CareDx considers itself "an international transplant diagnostics company with product offerings along the pre- and post-transplant continuum." In that (somewhat hyperbolic) vein, the company mainly provides two diagnostic test services, AlloMap and AlloSure, as well as HLA-typing products used by transplant clinics to match donor organs with recipients. AlloMap is a gene expression test used in routine screening of heart transplant recipients in order to rule out acute cellular rejection. The test was first commercialized in 2006 and has been moderately successful, though bound by the relatively small number of heart transplants performed in the US each year (~2,000). On its own, AlloMap was never more than marginally profitable, and we think its stand-alone value is negligible. The same can broadly be said for the company's HLA-typing business.

AlloSure, the primary subject of this report, targets the much larger kidney transplant market (21,167 transplant procedures were performed in the US in 2018).[5] By measuring the levels of donor-derived cell-free DNA (dd-cfDNA) in the transplant recipient's blood, AlloSure aims to be an accurate biomarker of kidney rejection, helping physicians "detect rejection of a donated organ earlier and more accurately" than the current standard of care, and "reduce the use of invasive biopsies,"[6] which are currently the only way to accurately assess whether a patient is suffering rejection.

Rejection, though, is a loaded term. In the general sense, it describes the phenomenon of the transplant recipient's immune system attacking and damaging the implanted kidney. But there are a few different kinds of rejection:[7]

[5] According to the United Network for Organ Sharing
[6] CareDx 2018 10-K, Item 1, Company Overview
[7] This discussion keeps the descriptions of the various types of rejection relatively simple. For detailed descriptions of the histopathology of various types of kidney rejection, see the review of the Banff 2017 conference here.

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- T-Cell-Mediated Rejection (TCMR/CMR) – also called cellular rejection, is generally marked by inflammation of kidney tubules and interstitial matter. In more severe cases, the inner arterial wall of the kidney becomes inflamed. In less severe cases, where the tubule/interstitial inflammation is minimal, cellular rejection can be labeled "borderline".
- Acute Antibody-Mediated Rejection (AMR/ABMR) – is marked by 1) inflammation of the vasculature of the kidney and 2) antibody-caused injury[8] to the renal endothelium (the interior walls of the blood vessels running through the kidney). True to its name, AMR is almost always accompanied by donor-specific antibodies (DSA, or antibodies that specifically target the unique cellular receptors associated with the donated kidney).
- Chronic AMR – is similar to acute AMR, but is labeled "chronic" if, based on the examination of the biopsy tissue, the damage is so severe that it's clear that the immune system attack has been ongoing for a while.

Diagnosing Rejection

The precise parameters of a kidney rejection episode – i.e., the type of rejection (AMR vs. CMR), the immune processes responsible, the parts of the kidney that are being damaged, etc. – are only discoverable via biopsy. But kidney biopsies are *not* normally a routine monitoring mechanism because performing them regularly on every single transplant recipient is seen as overkill. While some transplant clinics *do* perform such "protocol biopsies,"[9] most clinics monitor kidney function through routine measurement of serum creatinine and, to a lesser extent, albumin in the urine, both of which are cheaply and accurately obtainable. Healthy kidneys filter creatinine from the blood while allowing protein to remain in the blood stream, so elevated serum creatinine levels or protein in urine (proteinuria) signal impaired kidney function.

After consideration of patient-specific factors and ruling out other potential causes of abnormal creatinine or proteinuria, if kidney rejection is suspected, a biopsy is performed. The biopsy examination of the kidney tissue by a pathologist is the ultimate arbiter of whether the patient is suffering from transplant rejection.

But relying on kidney function as the first sign that a transplant might be rejecting is less than ideal. First of all, it's not very "specific," which means that decreased kidney function *could* be a sign of rejection, but it could also be a sign of other problems such as dehydration, infection, or other kidney injuries. Biopsies performed due to elevated creatinine/proteinuria therefore come back negative for rejection over half the time.

Kidney function is also not a very "sensitive" indicator of kidney rejection, which means that there's a lot of rejection taking place that doesn't get picked up by serum creatinine measurement. Transplant clinics that perform protocol biopsies have published studies on the

[8] Generally indicated on a biopsy by a phenomenon called C4d staining

[9] Protocol biopsies are biopsies performed routinely for screening purposes, generally in the year after the transplant surgery. By contrast, biopsies performed due to suspicion of rejection or other kidney injury are called "indication biopsies." Protocol biopsies mostly come back negative, are expensive, carry a small risk of severe bleeding, and would be a logistical impossibility for most transplant clinics to perform.

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frequency of rejection diagnoses that result from these biopsies, and it's clear that plenty of rejection episodes happen with *no falloff in kidney function*. The simplest explanation for this is that a loss of kidney function is often the *end-result* of rejection, but the actual immune system attack begins earlier and only manifests itself in impaired kidney function after a sustained period of activity. It's also possible for immune activity to be *temporarily* heightened, leading to a case of *temporary* rejection that never advances to the point of declining kidney function.

Kidney rejection in the absence of reduced kidney function is called "subclinical rejection" because of its ability to evade detection. It is generally believed that enough time spent in a state of subclinical rejection eventually results in chronic AMR or severe TCMR.[10] Over the last decade, multiple studies of protocol biopsy data have estimated the incidence of subclinical rejection to be anywhere in the range of 10-30% of biopsy samples.[11] That means much, maybe most, of kidney rejection goes undetected and untreated, potentially with negative consequences for long term graft survival.

Another problem with diagnosing "rejection" is that each type of rejection – TCMR vs. AMR vs. Chronic AMR – is treated differently. Even if there were a test that could perfectly discriminate "rejection," a biopsy would still be necessary for a more granular diagnosis that would inform the subsequent treatment.

Cell-Free DNA

The limitations of kidney function markers like creatinine and proteinuria have been understood for decades. But no noninvasive diagnostic test or screening protocol has been shown to improve the means of detecting rejection, either through avoiding unnecessary biopsies (increased specificity) or by identifying subclinical rejection (increased sensitivity). AlloSure is really the first attempt at improving upon the long-standing status quo to be studied on a large scale.

AlloSure is CareDx's brand name for a test that measures the proportional quantity of donor-derived cell-free DNA (dd-cfDNA) in a transplant recipient's bloodstream. cfDNA is freely circulating DNA that's released from the cell nucleus upon cell death and ends up in the bloodstream. There's always some amount of cfDNA in a person's blood stream, a natural result of the perfectly normal process of apoptosis. Over the past decade, fetal cfDNA in the blood of expectant mothers has been tested in order to detect potential genetic disorders in the fetus. Tumor cfDNA has also been used more recently as a "liquid biopsy" in a variety of oncologic applications, including as a potential marker of residual disease after tumor resection and as a trove of potentially useful genomic information pertaining to the cancer.

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[10] Mehta R, Sood P, Hariharan S. Subclinical Rejection in Renal Transplantation: Reappraised. *Transplantation.* 2016;100(8):1610-1618.

[11] Ibid. See also Friedewald, JJ, Kurian, SM, Heilman, RL, *et al.* Development and clinical validity of a novel blood-based molecular biomarker for sub-clinical acute rejection following kidney transplant. *Am J Transplant.* 2019; 19: 98-109.

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In the transplant setting, the goal of a dd-cfDNA test is to quantify the proportion of cfDNA in the transplant recipient's bloodstream that's coming directly from the donated kidney. The logic is that the DNA of kidney cells, which are quite literally from another person, is different than the DNA of the transplant recipient. If the proportion of the *donor* cfDNA relative to *native* cfDNA is abnormally high in the blood, that would indicate some sort of injury to the kidney that's resulting in an elevated rate of kidney cell death. In theory, the only kind of injury that would cause that sort of event cascade is kidney rejection.

The idea of quantifying the proportion of dd-cfDNA as a marker of kidney injury was first hypothesized in the late 1990's by Dennis Lo and his team at the Chinese University of Hong Kong. As the costs of genetic amplification and sequencing technologies declined, the study of cfDNA in transplant recipients gained momentum. Stephen Quake, who would found ImmuMetrix to commercialize this technology (and then sell it to CareDx in 2014), published the first of many papers on cfDNA and transplants in early 2011 with the hopeful title, "Universal noninvasive detection of solid organ transplant rejection."[12]

In the almost-decade since then, hundreds of articles have been written about small-scale experiments in the use of dd-cfDNA to detect organ rejection. These papers can generally be described as hopeful, but inconclusive: they almost all find some positive correlation between levels of dd-cfDNA and transplant rejection, but the statistical relationship is rarely good enough to justify clinical usage (especially at scale). Nevertheless, there's almost always hope that with a bit of improvement and some large scale testing, the concept could work. Thus, in 2015, a review of cfDNA studies in the *American Journal of Transplantation* noted that

> Although dd-cfDNA is an interesting and promising marker of solid transplant organ health, much work still needs to be done before clinical implementation…In conclusion, whereas observational studies published so far point to dd-cfDNA as a promising marker in the transplantation field, randomized control studies are mandatory comparing a dd-cfDNA-based monitoring strategy with the standard post-transplantation monitoring in terms of graft and patient survival.[13]

With the achievement of Medicare coverage and reimbursement in mid-2017, large scale subsidized studies of dd-cfDNA became possible. The results don't bode well for AlloSure.

[12] Snyder TM, et al. Universal noninvasive detection of solid organ transplant rejection. *Proc Natl Acad Sci U S A. 2011*;108(15):6229–6234. doi: 10.1073/pnas.1013924108.
[13] Gielis EM, et al. Cell-Free DNA: An Upcoming Biomarker in Transplantation. *Am J Transplant* 2015;15:2541–2551.

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III. Clinical Data Show that AlloSure is Insensitive in Discriminating Kidney Rejection, with an Unacceptable Miss Rate

> *Screening tests have to be **really** cheap, and in kidney, serum creatinine and proteinuria are **very good** tests. They're actually excellent tests. And you're going to have to do **very** well to beat serum creatinine and proteinuria by enough to justify a thousand dollar test if you're doing screening.* [emphasis in the original]
>
> Dr. Philip Halloran, Inventor of the Molecular Microscope[14]

CareDx clearly positions AlloSure as a kidney rejection test that makes up for the weaknesses of serum creatinine, as the latter is "nonspecific as to cause and not sensitive, as serum creatinine may only be detected after significant and irreversible renal function loss has occurred." AlloSure is meant to be incorporated into the routine screening protocols used by transplant centers: "The AlloSure recommended testing protocol," according to CareDx, "includes 7 tests during the first year [post-transplant] followed by quarterly testing in the second year and beyond."[15]

To assess whether AlloSure is really an improvement over the current standard of care (SOC), which relies on creatinine and proteinuria measurement, two questions must be answered:

- Can AlloSure safely be used to avoid unnecessary biopsies? Over half of the biopsies triggered by impaired kidney function come back negative for rejection. Biopsies are invasive and carry some small risk of bleeding, so avoiding unnecessary biopsies, *without concomitantly avoiding the necessary ones*, would be a genuine improvement on the status quo. In statistical terminology: can AlloSure reduce the rate of false positives without introducing new false negatives?
- Can AlloSure be used to detect subclinical rejection, i.e., rejection that's currently missed by just testing for creatinine and proteinuria?

Based on our wide-ranging conversations with transplant physicians, as well as an exhaustive review of the clinical literature, the answer to *both* of the above questions is clearly, No. Let's start with the seminal AlloSure paper by Bloom *et al.*, which is used by CareDx as the basis for their marketing materials and "results interpretation" guide, both meant for physicians. The study focuses on 102 of the 384 patients in CareDx's DART clinical trial, which was conducted in order to validate AlloSure as an accurate measure of dd-cfDNA.[16] The 102 patients represent all the patients in the DART trial that had undergone an indication-biopsy (i.e., due to elevated

[14] Halloran is a world renowned transplant pathologist and the founding editor of the American Journal of Transplantation. Halloran's comments were made in a speech he gave to the Henry Ford Transplant Institute in June, 2017.

[15] Comments by CEO Peter Maag on 11/9/2017 during the 2017 Q3 Earnings Call

[16] The DART trial was not meant to evaluate the accuracy of AlloSure in detecting rejection. For that, CareDx is conducting the KOAR trial, the failure of which we argue can now be predicted with a high degree of confidence.

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creatinine/proteinuria) and also had an AlloSure test taken before the biopsy. In all, there were 107 paired AlloSure/biopsy results, all with a positive creatinine/proteinuria test.

Even with a biased sample (*every sample* was from a patient with some sort of kidney dysfunction as measured by creatinine/proteinuria), the data is damning. "Sensitivity" is a diagnostic test's ability to correctly detect patients who have the condition being tested for. Using 1% as the diagnostic threshold,[17] dd-cfDNA had a sensitivity of 59%. In other words, in the biopsies diagnosed as rejection, AlloSure would have detected only 59% of them, ***and would have missed 41% of rejection episodes***. Can AlloSure be used to avoid unnecessary biopsies? Maybe, but apparently at the cost of missing 40% of the *necessary* biopsies.

This goes directly to the heart of CareDx's major claims about AlloSure, namely that:

- It's more *accurate* than creatinine in discriminating rejection.
- It can therefore be used to rule out rejection if creatinine is positive but AlloSure is negative.

It's *technically* true that, in this particular study, AlloSure was more accurate than creatinine. But "accuracy" is a statistical term, an artifact of the number of false positives and false negatives. Accuracy doesn't account for the *severity* of the false result. In the case of kidney rejection, a false negative can result in organ failure, while a false positive means a relatively low-risk, but unnecessary biopsy. You'd rather over-diagnose than under-diagnose given the consequences. Creatinine indeed chalked up lots of false positives in the study (75%), while AlloSure had a lower rate of false positives (39%) and a *seemingly* low rate of false negatives (16%). CareDx touts the low false negative rate to show that AlloSure can be used to rule out rejection. But that's incredibly misleading: it's true that of 77 AlloSure tests that came back negative, "only" 12 tested positive for rejection on biopsy (16%). But missing 12 cases of rejection out of 27 is an unmitigated failure, and reveals the inability – and *risk* – of using AlloSure to rule out rejection.

We note that the numbers from the study actually *overstate* AlloSure's sensitivity because they don't account for cases of borderline rejection, a phenomenon that's frequently treated by nephrologists as low-grade rejection. Had borderline rejection been considered, AlloSure's miss rate would have been just over 60%.

In our discussions with transplant physicians, all but one – a co-author on the Bloom paper and a consultant to CareDx – maintained that a negative AlloSure couldn't reassure them in the presence of impaired kidney function; a biopsy would be essential in such a circumstance. Even physicians with financial ties to CareDx agreed that AlloSure can't be used as a rule-out method in the way that CareDx is marketing it, and that it would be dangerous to do so.

Because the Bloom study's patient population all tested positive for impaired kidney function, the study can't say much about subclinical rejection. But other studies of the DART data can:

[17] The 1% threshold is defined in terms of the proportion of cfDNA in the blood that can be identified as donor-derived. An AlloSure >1% comes back positive, and <1% it comes back negative. This is another significant bias of the study as the threshold was chosen by the authors on an *ex-post* basis, and conveniently optimizes for statistical accuracy.

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- In a paper published in the Journal of Applied Laboratory Medicine, Bromberg and co-authors looked at a different subset of the DART population: the 93 of 384 patients who demonstrated stable kidney function throughout the trial with no infections or other clinical events. All patients in the sample had 3 or more AlloSure tests, for a total of 380 AlloSure results, 3.7% of which were positive for rejection (i.e., expressed dd-cfDNA levels >1%).
- In a poster presented at the 2018 American Transplant Congress, Narayanan and colleagues examined yet another subset of the DART trial population: 202 of the 384 patients who were not diagnosed with rejection throughout the trial. This subset was more than double the size of that referenced in the previous bullet point, and included patients who at times tested positive for impaired kidney function, as well as patients who were biopsied for cause or suffered from graft infections. This group had a total of 1152 AlloSure results, 5.5% of which were positive for rejection.

The 3.7% and 5.5% positive rates in the aforementioned studies are indicative of a failure to detect subclinical rejection. Even assuming every single positive AlloSure result in these groups was accurate,[18] subclinical rejection rates are on the order of 10-35%, which means AlloSure is missing almost all it.[19]

AlloSure is fundamentally incapable of identifying the most common type of kidney rejection

The study published by Bloom *et al.* raises the possibility that AlloSure can more accurately identify Antibody Mediated Rejection (AMR) than T-Cell-Mediated Rejection (TCMR). While AlloSure identified only 59% of *all* rejection episodes in patients with impaired kidney function, it identified 81% of rejection episodes *classified as AMR*. The authors tersely note that the divergence of AlloSure accuracy "has potential to provide additional information…in the diagnosis, management, and treatment of AMR." We believe that the divergence – which has been substantially confirmed in recent clinical literature – amounts to an indictment of AlloSure's clinical utility as well as CareDx's entire business model.

The CareDx-sponsored study conveniently shows AlloSure's accuracy in discriminating AMR, but omits the obvious implication: AlloSure is incapable of detecting TCMR, with a hit rate of only 40%. The data from recent studies, as we will show, is even worse. The evidence suggests that AlloSure has a structural blind spot in detecting TCMR. Roy Bloom, the lead author on the study, recently hypothesized that the blind spot may be the result of structural differences between TCMR and AMR: AMR affects the microvasculature of the kidney, so the proximity of the damaged cells to the circulatory system allows for the emitted cfDNA to be picked up in a blood test. TCMR, though, is usually marked by tubular or interstitial inflammation, farther away

[18] Bloom *et al.* found a ~40% false positive rate in patients with impaired kidney function. Recent studies, discussed below, suggest AlloSure demonstrates higher rates of false positives in patients with stable kidney function.
[19] See Friedewald, *et al.*, referenced in note 10, and the references therein

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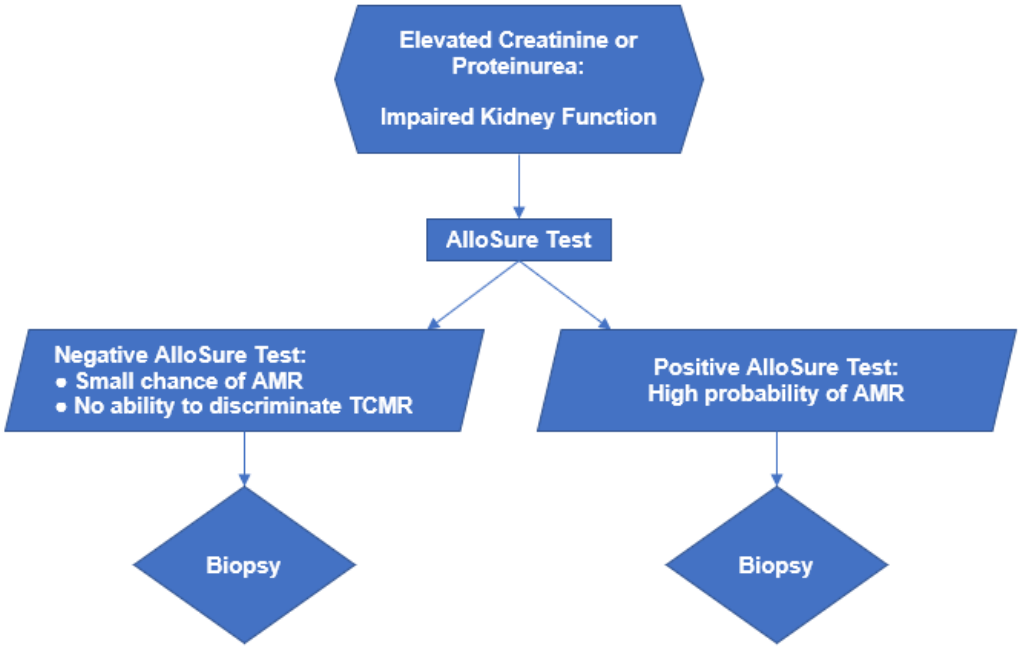
from the major circulatory highways. The emitted cfDNA in TCMR will have substantially degraded by the time it might reach the blood stream that's sampled in the blood test.

Whatever the reason, the problem with the increasingly acknowledged futility of AlloSure in TCMR is that distinguishing AMR from TCMR can only be done *after a biopsy sample has been examined*. The AlloSure test *may* tell you something about AMR, but it says *nothing* about TCMR, which means that in the case of impaired kidney function, a biopsy will still have to be performed. To simplify matters, consider the decision tree from the standpoint of a clinician:

Clinician Decision Tree in the Context of Impaired Kidney Function and AlloSure Testing



Source: Kerrisdale analysis

If a clinician is faced with elevated serum creatinine or proteinuria, the AlloSure test results are *thoroughly irrelevant*: they will *have* to conduct a biopsy if they want to know what's going on. There's almost no conceivable scenario in which AlloSure would be able to "reduce the use of invasive biopsies," as CareDx claims.

The inability to detect TCMR also undermines AlloSure's business model. The only way CareDx can claim a $2 billion market for AlloSure is if it's used as a screening test in the context of the company's recommended testing protocol. But the vast majority of rejection – especially in the immediate aftermath of the transplant procedure when the heaviest use of AlloSure is recommended – is TCMR, not AMR. AlloSure is therefore useless as a screening test, particularly in light of the $2,840 cost per test – ~300 times the cost of creatinine and proteinuria testing (combined), and 4 times the cost of a biopsy (including the pathology report).

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There are only two possible use cases that AlloSure's accuracy in AMR might justify: The first is monitoring the effectiveness of treatment *after* AMR has already been diagnosed via biopsy. The problem is that the market for AMR monitoring is about 5% of the overall kidney transplant population annually. Even at CareDx's inflated $2,840 per test (which, as we discuss below, we expect will come down dramatically), that leaves a total market size of ~$100 million.

The other potential use of AlloSure is as a screening test for subclinical AMR in sensitized patients who are at higher risk of AMR in the first place.[20] This market is a bit larger than the population of patients already diagnosed with AMR and could potentially reach about $400 million. The question is: can AlloSure detect subclinical AMR? Recently published studies suggest not.

Recent clinical literature paints a uniformly negative picture of AlloSure's clinical utility

As we discussed previously, Medicare coverage of AlloSure has spurred many transplant clinics around the country to conduct their own studies of AlloSure clinical utility. Three of these have, to varying extents, published their findings:

- This past March, Ed Huang and his colleagues published some of their findings from about 13 months of protocol AlloSure testing at Cedars-Sinai Medical Center in Los Angeles. The center conducted an AlloSure test on 352 transplant patients in the 13 month period, but only 63 patients were included in the study – those who were biopsied specifically as a result of impaired kidney function or elevated levels of donor-specific antibodies (DSA) in their blood.[21] The group found that "the distribution of dd-cfDNA was similar between Patients with isolated CMR [TCMR] and no rejection." In fact, the median dd-cfDNA in patients with TCMR was *lower* than the median in patients with no rejection at all, and 28% of the patients with no rejection tested *positive* with AlloSure, a fairly high rate of false positives.

[20] Sensitized patients are those who, before the transplant, are known to have donor-specific antibodies (DSA), or antibodies that will attack the transplanted tissue in the absence of appropriate immunosuppression.
[21] DSA is frequently, though not always, tested in sensitized patients at risk of AMR because of the strong association (~50%) between the presence of DSA and AMR.

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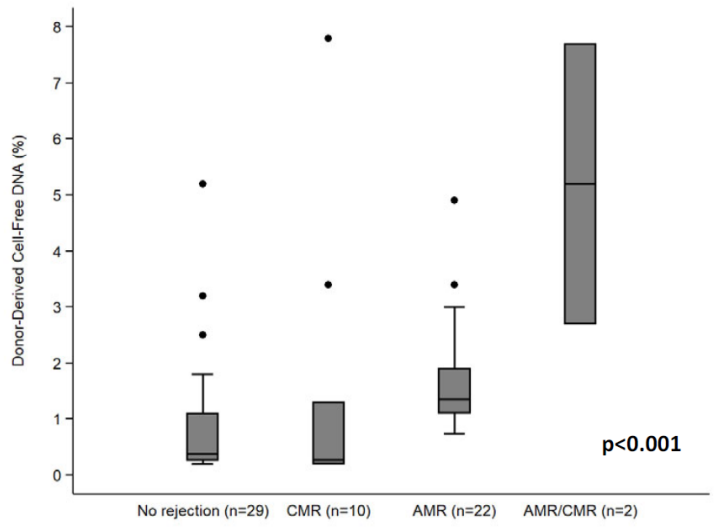
Distribution of Donor-Derived Cell-Free DNA Percentage by Biopsy Diagnosis



Source: Huang et al.

On TCMR, the paper concluded that:

> ***dd-cfDNA was not able to discriminate TCMR from no rejection***…The relatively low sensitivities observed in both studies [i.e., this and the Bloom study referenced above] *indicate that the dd-cfDNA test is susceptible to false negative results, particularly among cases of CMR…* ***levels of dd-cfDNA are not consistent across rejection types and levels observed in cases of isolated CMR can be indistinguishable from those without rejection.*** [Emphasis added]

On AMR, the paper concluded that "dd-cfDNA more reliably discriminated AMR and we consider that its greatest applicability will likely be for discerning the presence of AMR…" How might it do so? The implication is that it could help confirm the rare cases of AMR that are found in the presence of impaired kidney function but in the absence of DSA. A niche population indeed. Finally, on the topic of subclinical rejection, the paper admits that:

> dd-cfDNA was primarily assessed on a "for-cause" basis, where dd-cfDNA was assessed in the setting of suspected allograft rejection. *It is not yet known whether the prediction characteristics for dd-cfDNA will be similar when used to predict subclinical rejection when graft function is stable*. This is currently being assessed in a large, multicenter observational study using dd-cfDNA as part of routine surveillance for allograft rejection in kidney transplant recipients. [Emphasis and link added]

Curiously, though, the physicians at Cedars-Sinai did not publish any data on the other 289 patients with AlloSure results. Having spoken with physicians there, we understand that positive AlloSure results in the *absence* of impaired kidney function were also followed up

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with a biopsy. This is data that could help with assessing the utility of AlloSure in subclinical rejection. We suspect that the lack of published data is indicative of AlloSure's ineffectiveness in subclinical rejection.

- In a poster presented at the American Transplant Conference earlier this month,[22] Moinuddin and his colleagues compared the results of AlloSure with the diagnosis of the Molecular Microscope, a method that analyzes the mRNA in a biopsy sample to arrive at a rejection diagnosis. The study used 50 "for-cause" biopsy samples taken in the context of impaired kidney function. Interestingly, the sample of patients in this study included an abnormally high number of AMR cases (20) and only 2 cases of TCMR. Even so, AlloSure's sensitivity here was only 59%, unacceptably missing 9 of the 22 rejection cases. If anything, this small scale study might cast some doubt on AlloSure's utility even in niche cases of AMR diagnoses.

- The University of Colorado (CU) is in the midst of conducting a study on 150 transplant patients in which the recommended AlloSure testing protocol was used. The study began in January of 2018, and Stites and his colleagues presented interim data (from 1/1/2018 through 8/31/2018) at the American Society of Transplantation Summit in February of this year. The study is particularly interesting because CU has a protocol biopsy routine in which it performs a biopsy on all patients 3 months post-transplant, allowing for some assessment of AlloSure in subclinical rejection.

  Of 19 indication-biopsies with a paired AlloSure result, 4 were diagnosed as rejection by the biopsy, but only 2 of these tested positive with AlloSure. Of 91 protocol biopsies with a paired AlloSure result, 3 AlloSure results were positive, but all 3 were false positives. Meanwhile, 1 of the 91 biopsies was diagnosed as subclinical rejection, but AlloSure tested negative in that one. In other words, *in the population of protocol biopsies at CU, AlloSure had a 0% hit rate*. Finally, 4 patients were biopsied for a positive AlloSure test in the context of normal kidney function, but only one of those biopsies resulted in a rejection diagnosis. The results are summarized in the table below:

[22] The abstract can be found here.

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Distribution of Donor-Derived Cell-Free DNA Percentage by Biopsy Diagnosis

Reason for Biopsy	Sample Size	Biopsy-Diagnosed Rejections	Positive AlloSure Tests	AlloSure Hit Rate
Impaired Kidney Function	19	4	2	50%
Protocol Biopsy	91	0	3	0%
Protocol Biopsy	91	1	0	0%
Positive AlloSure w/Normal Kidney Function	4	1	4	25%

Source: AST Transplantation Summit Program Guide, Abstract #40

Imagine spending $1.4 million on AlloSure tests in the span of 8 months and finding only one incremental case of rejection that's potentially just statistical randomness (in cfDNA sampling). In total, 502 dd-cfDNA samples were collected from the 150 patients, with 5% of the samples (25) having dd-cfDNA values >1%, i.e., testing AlloSure-positive for rejection. Once again, that 5% number suggests that there's subclinical rejection (past the 3-month mark) that's not being picked up by AlloSure.

In a more recent presentation by the group at the University of Colorado at the American Transplant Congress, a different set of results was presented. The sample set in this study was composed of 70 biopsies performed on patients whose blood tests came back positive for DSA, indicating risk of AMR. Of these, 39 biopsies were diagnosed as AMR. Not all the DSA tests were paired with an AlloSure test, but in those that were, AlloSure correctly identified only 43% of rejection cases. Which begs the question – why perform a $2800 AlloSure test when it will miss over half the cases identified by a $755 DSA blood test?

To summarize: AlloSure is anatomically incapable of detecting the most common form of kidney rejection, TCMR, even in the presence of impaired kidney function. In the case of AMR, it's impossible for AlloSure to be used as a rule-out mechanism in the presence of impaired kidney function or a positive DSA test, so a $2 billion market opportunity built on mass AlloSure screening is, at best, a delusion. Finally, it's almost certain that AlloSure cannot identify subclinical AMR in any systematic way, though it's worth noting that the market for AMR screening is comprised of highly sensitized transplant recipients, which represent – at most – about 15% of the total kidney transplant population.[23]

[23] Based on the granular data reported by the Organ Procurement and Transplantation Network

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IV. AlloSure Revenues Overwhelmingly Come From Protocol Usage in Clinical Testing, Which is Suffering 20-30% Quarterly Attrition

Despite its fatal flaws, CareDx has been able to generate a lot of buzz regarding AlloSure, successfully steering the test to ~$45 million in annualized revenues as of the most recent fiscal quarter. But the foundation of AlloSure's success is surveillance usage in clinical studies like the ones taking place at Cedars-Sinai and the University of Colorado. CareDx likes to boast that surveillance usage "helps build the recurring revenue effect of AlloSure" but we think that it's helped build an AlloSure house of cards.

To put AlloSure's success in context, recall that cfDNA has been the subject of intense study and speculation in the transplant community for over 20 years. The Quake lab at Stanford lent cfDNA a Silicon Valley halo by publishing a small study of its potential in the heart transplant setting in early 2011, and hundreds of small scale studies followed over the years. Strangely, Quake and Snyder started a company called ImmuMetrix to commercialize cfDNA testing in transplants but sold it to CareDx in 2014 for $17 million in (then-privately-held) stock, apparently judging the opportunity not sufficiently exciting. A year after acquiring ImmuMetrix, CareDx began its DART clinical trial with a target enrollment of 200 patients, the (then) largest ever study of cfDNA in transplants.

While much of the cfDNA research to that point had been in heart and lung transplants, CareDx focused the DART trial on kidneys because only kidney transplants offered the potential volumes that would make for a lucrative business. Kidneys are also unique in that medical care for 3 years post-transplant is entirely covered by Medicare, so broad payor coverage for a rejection test would essentially require only Medicare to assent.

CareDx was also aided by the unique status of diagnostic tests with regulatory bodies. As a Laboratory Developed Test (LDT), AlloSure didn't need FDA approval; and to obtain payor coverage, CareDx went through MolDX. The MolDX (Molecular Diagnostic Services) program was set up in 2011 to manage the growing number of genetic and molecular diagnostic LDTs and is run under the auspices of Palmetto GBA, a Medicare Administrative Contractor (MAC) in the Southeast. Most other MACs in the country have outsourced LDT coverage decisions to MolDX, so the program is effectively a gateway to national coverage and reimbursement for LDTs. To get a Local Coverage Determination (LCD) from MolDX, a test must pass a technical assessment and demonstrate "analytical validity, clinical validity, and clinical utility."

MolDX will typically grant an LCD even with limited evidence of clinical utility, conditional upon further research that's expected to prove clinical utility. That's precisely the case with the LCD for AlloSure, finalized on October 2, 2017, which states that MolDX

> recognizes that the evidence of clinical utility for the use of AlloSure in its intended use population *is promising at the current time*. However, this contractor believes that

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> forthcoming prospective clinical studies *will demonstrate improved patient outcomes*. *Continued coverage for AlloSure testing is dependent on annual review by this contractor of such data and publications*. [emphasis added]

For the time being, though, AlloSure is covered and reimbursable for almost any kidney transplant recipient within 3 years of the transplant procedure.

With a decade's worth of curiosity on cfDNA and comprehensive Medicare coverage, the ideal conditions were in place for CareDx to market AlloSure to transplant physicians. This was the first time that a "promising" noninvasive biomarker for rejection could be studied at scale, *and at no cost to the provider*. In fact, the more widely studied, *the more revenue the provider would be generating*, as every test would be reimbursed by Medicare at a rate of $2,840. CareDx would effectively be profiting from studies being undertaken to determine whether it actually works.

The company immediately began enrollment on a massive 1000-patient clinical trial, which it expected to "include approximately 10,000 reimbursed AlloSure tests over the next 3 years, thus representing incremental AlloSure volume as well as another revenue driver going forward."[24] Besides CareDx's official clinical trial, AlloSure reimbursement allowed any transplant center interested in cfDNA research to conduct its own single-center study. Given a deep-rooted culture of such protocol studies in the transplant space, it's not surprising that many transplant centers have launched AlloSure studies outside the confines of CareDx's clinical trial.

Of course, CareDx had already further stacked the odds in its favor by establishing research and consulting relationships with influential academic transplant physicians at many of the largest transplant clinics in the country. By our latest count, CareDx has financial relationships – research funding, consulting agreements, honoraria, and/or speaker fees – with transplant physicians in clinics comprising 23% of the total kidney transplant volume in the US. There's nothing necessarily nefarious about this, but it certainly helps when you consider that CareDx's business model is built on populating patient registries in order to study AlloSure as a surveillance mechanism. By CareDx's admission (see the table below), over 90% of AlloSure revenue consistently comes from patients on an AlloSure surveillance protocol, and these are overwhelmingly within the framework of AlloSure studies.

In medicine, commercialization is usually *preceded* by evidence that the product actually works. CareDx figured out a way to turn that on its head, commercializing the product first, and then generating revenue by studying whether it works. Natera's Chief Commercial Officer, in a conference call announcing a competing cfDNA test last year, declared that "we think the coverage-with-evidence-development process is very favorable because in fact you get paid while you're completing your clinical utility work." Ironically, the results of the clinical utility work, as previously discussed, are not very good. We're not the only ones to notice: based on management disclosures of patient counts since AlloSure testing began, we estimate the attrition rate of patients on an AlloSure surveillance regiment has been approximately 25% *per*

[24] 11/9/2017 – CareDx Fiscal 2017 Third Quarter Earnings Call

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quarter.[25] Consistent with the "evidence-development," doctors are apparently not finding AlloSure to be useful in treating patients.

Historical AlloSure Patient Data (Quarterly)

	2017 Q4	2018 Q1	2018 Q2	2018 Q3	2018 Q4	2019 Q1
Centers offering AlloSure	32	52	76	96	100	101
Tests Administered						
Surveillance Tests	163	892	2,076	3,644	4,365	5,074
% Growth (qoq)		*446%*	*133%*	*76%*	*20%*	*16%*
Ad-hoc tests	119	159	224	64	210	636
Total AlloSure Tests	282	1,051	2,300	3,708	4,575	5,710
Patient Count						
Surveillance Patients (SPs)						
Gross new SPs	131	682	1,101	1,862	1,301	1,430
Attrition	16	114	308	602	847	976
Net New SPs	115	568	793	1,260	454	454
End-of-Quarter SPs	115	683	1,476	2,736	3,190	3,644
Non-Surveillance Patients	119	159	224	64	210	636
Total Quarterly Patients	250	842	1,700	2,800	3,400	4,280
Cumulative Patients						
SPs	131	813	1,915	3,777	5,077	6,507
Non-SPs	119	278	502	566	776	1,412
Total Cumulative Patients	*250*	*1,091*	*2,416*	*4,342*	*5,853*	*7,919*
Avg Quarterly Attrition of Surveillance Patients				***25%***		
Tests/SP	1.42	1.31	1.41	1.33	1.37	1.39
Surveillance Test Share	58%	85%	90%	98%	95%	89%

Source: CareDx filings, Management quarterly commentary, Kerrisdale estimates and analysis

[25] To illustrate: As of the end of the 2018 Q4, management stated that "Since launching AlloSure in October 2017, we have provided results to over 6,000 patients which equates to approximately 3% of the total number of living kidney transplant patients." Just a quarter later, management stated that "Since launching AlloSure in October 2017, we have provided results to over 8,000 patients, which equates to approximately 4% of the total number of living kidney transplant patients."
In other words, the incremental cumulative patient count increased over the quarter by 2,000 (see the "Total Cumulative Patients" estimate in the table), yet the number of surveillance patients (explicitly disclosed) increased by 454. After accounting for the non-surveillance tests, the implication is that about 1,000 patients dropped out of the surveillance pool over the quarter.
Similarly, at the end of 2018 Q3, management stated "In the last 12 months, we have provided 2% of kidney transplant patients in the U.S. with an AlloSure result." By the end of Q4, the cumulative proportion was 4%, double the percentage 6 months prior, even as the surveillance patient population only increased by about a third.

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It's only a matter of time before it becomes impossible for AlloSure to keep up with such a staggering rate of attrition. Already, as the table above shows, the cracks in the foundation are beginning to show: the number of clinics using AlloSure has been flat for the last 6 months and net new surveillance patients have fallen off dramatically since peaking in the third quarter of 2018. CareDx has also been stretching to make its numbers by pushing for more non-protocol testing (as demonstrated by the jump in non-surveillance patients in the most recent quarter), but that's ad-hoc usage that's unlikely to recur and potentially eats into their surveillance market.

Finally, it's worth noting here that CareDx's recommended testing protocol is very front-end loaded: 5 tests in the first 6 months post-transplant, and quarterly afterwards. Considering new surveillance patients peaked in the third quarter of 2018, we should begin to see a decline in tests-per-surveillance-patient in the second or third quarter of this year, which will make the revenue treadmill harder to outpace. Already we calculate that sequential growth in the absolute number of surveillance tests in the most recent quarter was the lowest since AlloSure was introduced, and the sequential growth rate has decelerated dramatically. As we describe below we expect that competition will exacerbate the situation.

V. AlloSure is Vulnerable to Both Increasing Competition and Medicare Risk

AlloSure faces significant competition in the near term and almost certain obsolescence over time

The most immediate competitive threat faced by AlloSure is from Prospera, a dd-cfDNA assay marketed by Natera, a company with a long history of cfDNA testing in prenatal and oncologic settings. Natera published a validation study of Prospera in February of this year, and received a draft LCD from MolDX in late March. The company had previously published a study detailing the test's ability to discriminate kidney rejection, in which the authors purported to show that Prospera can accurately identify all kinds of kidney rejection, including TCMR and subclinical rejection.

Based on our reading of the study and discussions with several well-respected transplant researchers, we're skeptical of Prospera's ability to detect rejection as well as the study indicates.[26] Nevertheless, it's likely that Prospera is just as good as AlloSure given that both tests are measuring the same thing, and Prospera is based on the same technology and process that Natera has long successfully used in its prenatal testing. Prospera also targets 13,392 SNPs while AlloSure makes do with only 266, and while that's not *nearly* as significant

[26] Several valid objections to the study appear in CareDx's lawsuit against Natera, though ironically, many of the objections CareDx raises are just as easily applicable to Bloom's AlloSure study and CareDx's marketing practices. Still, it's obvious that the study is methodologically weaker than Bloom *et al.*

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as it sounds, it's possible that Prospera will turn out to be more accurate than AlloSure in measuring dd-cfDNA.[27]

We expect the proposed LCD will be approved by the end of the summer and take effect by the end of the third quarter, at which point Prospera will be covered and reimbursed by Medicare. Natera has deftly prepared for that milestone by partnering with Thermo Fisher's One Lambda to co-distribute Prospera. One Lambda is the dominant testing and equipment vendor to transplant clinics, providing an array of organ matching tests as well as antibody detection products. Given the role of antibody detection in diagnosing AMR, and One Lambda's leading market position in rejection prevention and monitoring, we expect Prospera will find a receptive audience, especially among physicians unimpressed with AlloSure, but still holding out hope for cfDNA. We don't think they'll find Prospera to be any more helpful, but it will be enough to make a dent in AlloSure.

Natera also has a much lower cost structure for Prospera than CareDx has for AlloSure. We estimate that the unit-level cost of an AlloSure test is in the range of $500-600, while Natera expects to leverage its expertise in fetal cfDNA to reach a Prospera "COGS below $200 per [blood] sample".[28] Natera has already stated that it expects Prospera to initially be reimbursed at the same rate as AlloSure, but we expect that price competition will gradually emerge. As discussed previously, if cfDNA has *any* utility in transplant patients, it will be in patients with AMR, which overwhelmingly occurs *after* Medicare coverage of transplant patients ceases 3 years post-transplant. In pursuit of coverage and reimbursement from commercial payors, price will undoubtedly play a role in the competition between tests that evaluate the same exact thing and Natera's large fetal cfDNA business gives it economies of scale that CareDx lacks.

Because of PAMA rules, Medicare diagnostic reimbursement rates are tethered to commercial reinsurance rates, and any price competition motivated by commercial coverage considerations will, by definition, translate into large declines in Medicare reimbursement for both AlloSure and Prospera.[29] Consider that Natera's current tests for aneuploidy and microdeletion, which use the same underlying methods as a dd-cfDNA test but with greater precision, are currently reimbursed at a rate of about $800 by Medicare. We would expect reimbursement of a dd-cfDNA test to end up in around the same range if it does indeed turn out that it's useful for monitoring patients with AMR.

Even then, though, the utility of dd-cfDNA is likely to be short-lived. After all, a dd-cfDNA measurement simply detects the *existence* of donor-derived DNA fragments in a patient's blood stream, on the theory that abnormally large quantities are indicative of transplant injury. But the test does nothing to interrogate, or even describe, the genetic material in ways that could

[27] SNPs are Single Nucleotide Polymorphisms – the several million single nucleotide locations that are known to vary among humans. 266 SNPs clearly measure dd-cfDNA accurately *enough*, but it's possible that 13,392 are somewhat more accurate. The only way to ever really know would be a head-to-head prospective trial, which is not currently planned.

[28] Natera commentary on the 6/27/2018 Investor Call aimed at discussing the transplant opportunity.

[29] "Effective January 1, 2018, the payment amount for most tests equals the weighted median of private payor rates."

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illuminate the condition of the organ. In recent years, researchers have begun to search for blood-based gene expression profiles (GEPs) that could be used as markers of different kinds of organ injury. On the same day as the proposed LCD for Prospera was released, the first such blood-based genomic test – TruGraf – was also the subject of a proposed LCD. TruGraf was developed, and rigorously validated, specifically as a test for subclinical kidney rejection. The test also performed well in a prospective clinical trial, as well as in two prospective follow-up studies. The company that developed TruGraf, Transplant Genomics, is also in the process of developing a similar GEP test to detect and monitor acute clinical rejection.

In theory, the promise of genomic tests like TruGraf lies in their power to more specifically identify a particular kind of injury or illness because they can decipher relevant gene expressions with granularity. The catch has been in the definition of "relevant" as it's not always clear which genes are worth sequencing, but TruGraf is a good indication that it can be done rigorously and that the technology is rapidly improving. AlloSure, by comparison, can't say anything about genetic expression because cfDNA fragments are too short to interpret given their already degraded form. dd-cfDNA is simply too blunt an instrument to be widely used as an expensive LDT.

The TAM for AlloSure is a fraction of CareDx's claims and Medicare coverage will be scaled back accordingly

CareDx claims that the total addressable market (TAM) for AlloSure is over $2 billion. It gets to that number by multiplying the estimated number of people in the US living with a kidney transplant (~190,000) by the "recommended" number of annual AlloSure tests (5 in the 6 months post-transplant, once per quarter thereafter), and using the current Medicare reimbursement rate of $2,841 per test. But consider that total annual healthcare expenditures on transplant patients in the US are approximately $7 billion.[30] A TAM that would comprise 25% of the entire kidney transplantation market is laughable. After all, even if AlloSure worked as advertised, it's just a screening test that *might* inform the course of treatment.

On a per-patient basis, the TAM assumptions are even more absurd. The annual cost of medical care post-transplant is about $25 thousand dollars *on average*.[31] But that includes the elevated expenditures in the immediate aftermath of the transplant, which have been estimated to reach $50-75 thousand in the 6 months after the procedure. Thereafter, the annual cost of care is in the $10-15 thousand range. At $2,841 per test, and four tests per year, CareDx implicitly expects investors to believe that *doubling* the annual cost of care for transplant

[30] Total Medicare expenditures are ~$3.5 billion while Medicare accounts for about 55% of total expenditures on transplant patients.

[31] Data is from UCSF. Medicare expenditures per transplant patients are about $35 thousand per year, but that includes expenditures on the actual transplant procedure. Adjusting for that, the average Medicare expenditure per transplant patient approximates the UCSF estimate of $25 thousand, which includes both patients treated immediately post-transplant and patients treated in the years that follow.

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recipients by administering AlloSure tests is a legitimate possibility. Even in the absence of poor trial results and massive attrition, that proposition seems ridiculous.

But those trial results are important in quantifying the realistic TAM for AlloSure because they clarify the potential use cases for dd-cfDNA. It's pretty clear that AlloSure can't be used to detect or rule out rejection when used as a screening test, so estimating a TAM based upon its use in that capacity – as CareDx does – is fanciful. Given the *potential* utility of cfDNA in the context of AMR, the two use cases discussed previously – AMR monitoring and, much more speculatively, AMR screening – amount to a TAM of ~$500 million in the best case. Even that – at 25% of CareDx's estimate – is doubtful: AMR screening is likely to wind up the domain of genomic tests like TruGraf that – unlike AlloSure – are sensitive to subclinical AMR, and the price tag on dd-cfDNA is almost certain to decline.

The trial results will also have regulatory implications. As the MolDX LCD implies, the use case boundaries defined by the KOAR trial results will determine the eventual Medicare coverage of AlloSure. In our view, the total failure of AlloSure in the context of TCMR makes CareDx's recommended testing protocol a non-starter for Medicare, particularly considering that it would increase Medicare expenditures on transplant patients by 25% if implemented broadly. The entire point of broad MolDX coverage was to allow for the testing of clinical utility, and when that testing definitively comes up empty, the coverage will be rapidly scaled back. We expect that Medicare will eventually cover dd-cfDNA in cases of AMR or suspected AMR. That *would* be the death knell for AlloSure, but it looks like attrition and competition will get there first.

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VI. Valuation and Conclusion

CareDx's valuation, at 18.4x trailing revenues, makes little sense. Over half of CareDx's revenue in its most recent quarter came from its non-AlloSure businesses, which have negligible value. Consider that before AlloSure's Medicare approval, the company's enterprise value languished in the $50-100 million range for about three years after the company's IPO. Even if we add the $50 million of Allenex enterprise value acquired in 2016, the goodwill of which has been written-off given the business's lack of profitability, the total value of CareDx's non-AlloSure operations, plus cash, is not much more than $3.50/share. The valuation of AlloSure, then, is closer to 48x trailing revenues and over 30x the most recent quarter's annualized revenue run-rate.

CareDx and AlloSure Current Valuation

(in mm, except for per-share figures)		
Value of AlloMap and legacy HLA Matching	$	100
Value of Allenex		50
Net Cash		57
Value Ex-AlloSure	$	207
Market Capitalization	$	1,685
Implied AlloSure Value		1,477
TTM AlloSure Revenue		31
Revenue Multiple (TTM)		***47.7x***
Q1 AlloSure Revenue Annualized		44
Revenue Multiple (Q1 Annualized)		***33.3x***

Source: Kerrisdale estimates and analysis

Valuing CareDx like Natera

(in mm, except for per-share figures)		
dd-cfDNA Total Addressable Market	$	200
TAM Penetration at Maturity		75%
CareDX Market Share		60%
AlloSure Revenues at Market Maturity	$	120
EV/Revenue Multiple		4.0x
AlloSure Value	$	480
Years to Market Maturity		5
Implied AlloSure Value	$	298
Implied CareDX Value		505
Per Share:	**$**	**11.22**
Downside:		*-70%*

Source: Kerrisdale estimates and analysis

The relatively recent success of cfDNA in prenatal and cancer applications has allowed for anticipation about applications in transplant diagnostics to go almost totally unchecked. But there are critical distinctions between kidney rejection screening, on the one hand, and prenatal and cancer screening on the other. In prenatal screening, Natera's cfDNA tests boast sensitivity and specificity percentages in the high 90's. In cancer screening, cfDNA represents a substantial improvement over imaging because cfDNA is used when the cancer is simply undetectable using imaging, which is the incumbent standard of care. Crucially, in the transplant setting, cfDNA demonstrates poor sensitivity, particularly as compared to the exponentially cheaper current standard of care.

The expectations implied in CareDx's valuation are completely unmoored from reality. At best, AlloSure may be used in the niche application of AMR treatment monitoring, a market no larger than $100 million at current AlloSure pricing, and probably less than half that size once pricing inevitably compresses. More likely, AlloSure will be a historical footnote in the trajectory of transplant diagnostics – a "promising" biomarker with a solid rationale that was just not good enough to be useful. With CareDx's fate inextricably linked to AlloSure's, the prognosis for the stock price is dim.

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