KOL Event

Transplant Rejection Testing

September 22, 2021

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Agenda

Time	Presentation title	Speaker	Duration
1:00 PM ET	Opening introduction to OCX/Transplant Opportunity	Ronnie Andrews, President and CEO	10 minutes
1:10 PM ET	Donor-derived cell-free DNA testing in organ transplantation	Michael Oellerich, MD, Hon MD, FAACC, FAMM, FFPath (RCPI), FRCPath	30 minutes
1:40 PM ET	OCX TheraSure Assay Overview	Ekkehard Schuetz, MD, PhD, FAACC, SVP, Therapeutic Monitoring R&D at Oncocyte	20 minutes
2:00 PM ET	Live Q&A	Dr. Oellerich, Dr. Schuetz, and Ronnie Andrews	20 minutes
2:20 PM ET	Closing remarks	Ronnie Andrews	5 minutes
2:25 PM ET	Event conclusion		

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Michael Oellerich, MD, Hon MD, FAACC, FAMM, FFPath (RCPI), FRCPath

Dr. Oellerich is a chemical pathologist and currently a Distinguished Research Professor at the Department of Clinical Pharmacology, University Medical Center (UMG) of the George-August-University Göttingen, Germany. From 2012 to 2017, he had an appointment as a Lower Saxony Distinguished Professor. He was chairman of the Department of Clinical Chemistry/Central Laboratory at UMG from 1991 to 2012. He received Fellowships of the Royal College of Pathologists (FRCPath) in 2006, of the Faculty of Pathology of the Royal College of Physicians of Ireland [FFPath (RCPI)] in 2006, of the AACC Academy (FAACC) of the American Association for Clinical Chemistry in 2012, and the Academy of Medicine of Malaysia (FAMM) in 2014. Since 2013, he is a member of the Transplantation Advisory Board of Chronix Biomedical Inc., San Jose, CA, USA.

From 1996 to 1998, he served as Dean of the Faculty of Medicine and as the Deputy of the Chief Executive for Research and Teaching on the executive board for the Medical Center and Faculty of Medicine (1999-2004). He was President of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) (1997-1999), of the German Association for Laboratory Medicine (2001-2002), and the German United Association for Clinical Chemistry and Laboratory Medicine (2003-2005). Subsequently, he was Secretary-Treasurer of the World Association of Societies of Pathology and Laboratory Medicine (WASPaLM) (2005–2007), President (2009–2011), immediate past-President (2011–2013), and Director Europe (2013-2017). Since 2016, he is Executive Secretary of the International Society of Enzymology and, since 2017, Chief Research Officer of the Liquid Biopsy Center GmbH (LBC), Göttingen, Germany. From 1999 to 2010 he was a member of the Steering Committee of EUROLIFE, a network of European Centers of Excellence in life sciences. He served as External Examiner for the Second Professional Examination 2009/2010 of the Faculty of Medicine at the Chinese University of Hong Kong. He is an honorary member of the Romanian Society of Laboratory Medicine (Sibiu 2007), the Bulgarian Academy of Sciences and Arts (BASA) (Sofia 2012), and of IATDMCT (Salt Lake City, USA, 2013). He was Editor-in-Chief of the journal Therapeutic Drug Monitoring (2003-2018) and currently is Associate Editor of this journal. He was Associate Editor of Clinical Biochemistry (1996–2007), Associate Editor of Clinical Chemistry (2007-2013), and Guest Editor (Special Issues) of Clin Chim Acta 2012 and J Appl Lab Med 2020. He was on the Editorial Board of Clinical Chemistry (2002-2007; 2014-2016), and currently is on the Editorial Boards of Clinical Biochemistry as well as of J Mol Clin Pathol, Folia Med, Turk J Pediatr Biochem, and Indian J Clin Biochem. He is a member of the Advisory Boards of Ital J Lab Med and Braz J Pathol Lab Med.

His current research interests are in the field of therapeutic drug monitoring, with a particular focus on endogenous biomarkers to achieve personalized immunosuppression in transplantation (e.g., donor-derived cell-free DNA), as well as ctDNA as a “liquid biopsy” in cancer. Further topics include proteomics and analytical techniques (e.g., LC-MS/MS). He has authored more than 470 publications (articles contributed to scientific journals, book chapters, books edited). He received the following awards: Ludolf-Krehl prize of the S.W. German Society for Internal Medicine in 1971, the IATDMCT Award, Cairns (Australia) 1999, the IATDMCT Charles Pippenger Award for Outstanding Contributions to Therapeutic Drug Monitoring, Washington (USA) 2001, the 2002 Canadian Society of Clinical Chemists Travelling Lectureship Award, the Professor-Landbeck-Award of the Society for Thrombosis and Hemostasis Research, Hamburg (Germany) 2004, the Perth PathCentre Visiting Lectureship, Western Australia 2004, the WASPaLM Medal of Honor, Las Vegas (USA) 2011, the WASPaLM Gold Headed Cane, Quebec City (Canada) 2013, and the Sign of Honor, Professor Jordan Todoroff, of the BSCL, Sofia (Bulgaria) 2019.

Donor-derived cell-free DNA testing in organ transplantation

Michael Oellerich, MD, Hon MD
FAACC, FAMM, FFPath (RCPI), FRCPath
Distinguished Research Professor

Department of Clinical Pharmacology
George-August-University Göttingen
Germany

Donor-derived cell-free DNA as a "liquid biopsy" in transplantation

Key issues:

- Need for biomarkers to monitor graft integrity and to personalize immunosuppression
- Limitations of traditional approaches
- Rationale for using dd-cfDNA as a biomarker in transplantation
- Clinical validity of dd-cfDNA testing
- Benefits of dd-cf DNA testing / economic implications

Data from the US transplant registry

Transplants by the number:
33,610 patients per year
~ 316,000 living graft recipients

Shortage of donor organs:
Waiting list: ~ 124,000 patients

Shortage of transplant kidneys:
Premature deaths per year: ~ 5,000 to 10,000
Median waiting time: 3.6 years

Number of transplants in 2016

Kidney	Liver	Heart	Lung	Pancreas	Intestine
19,128	7,841	3,209	2,329	146 (PTA) 976 (all)**	67

Acute rejection at 1 y (%)

Kidney	Liver	Heart	Lung	Pancreas	Intestine
12.0	11.5 9.4-20.5*	20.2 18.7-24.0*	17.2 15.0-26.9*	16.5 (PTA) 15.6 (all)**	35.0

** Age dependent; ** PTA, SPK, PAK*

Held PJ et al, Am J Transplant 2016; 16: 877-885

OPTN/SRTR Annual Data Report 2016.
Am J Transplant 2018; 18 (S1): 1-503

Factors limiting long-term outcome

- Irreversible chronic allograft dysfunction
- Acute rejections contribute to poor outcomes
- Adverse effects of standard immunosuppression
  (e.g. nephrotoxicity, cardiovascular disease, opportunistic infection, malignancy)

- 10-year graft survival rates:
  Kidney: 55-69%, liver: 56%, heart 58%, lung: 30%
- Overall kidney graft failure within 5 years: 15-28%

→ Biomarkers needed to achieve personalized immunosuppression and reduce premature graft loss

Arnaud CH, C&EN 2018; https://cen.acs.org
Bouatou Y et al, Am J Transplant 2019; 19: 1971-1988

Tanriover B et al, Clin J Am Soc Nephrol 2016
Levitsky J et al, Clin Gastroenterol Hepatol 2017

Limitations of traditional graft monitoring

- **Biopsies:**
  - complication rate 1%; inadequate specimen in ~ 25%
- **Immunosuppressive drug monitoring:**
  - indicates toxicity; poor predictor of graft damage
- **Conventional biochemical markers unreliable in:**
  - HTx, LUTx, LTx
  - KTx:
    - Significant degree of graft damage already present by the time a rise in creatinine (SCR) is evident
    - SCR not specific for allograft injury (e.g. increase due to exsiccation, ACE inhibitors)

→ **Interventions may be too late to avoid graft injury/loss**

Bloom RD et al, J Am Soc Nephrol 2017; 28: 2221-2232
Knight SR et al, Transplantation 2019; 103: 273-283

Rodríguez-Perálvarez M et al, Transplant Int 2012; 25: 555-563
J Am Soc Nephrol 2005; 16: 1886-1903

Need for biomarkers providing clinically actionable information

- Early detection or exclusion of acute or chronic rejection as clinical features are unreliable
- Detection of asymptomatic graft injury including subclinical rejection before irreversible damage occurs
- Assessment of minimal necessary exposure (e.g. to guide tapering and prevent immune activation)
- Detection of under-immunosuppression (e.g. to decrease risk of transplant loss)
- Achievement of personalized immunosuppression to reduce premature graft loss
- Practicality: Reasonable TAT and cost

Schütz E, … Oellerich M, AACC San Diego 2017

dd-cfDNA ("liquid biopsy") – diagnostic tool for monitoring transplant recipients

Rationale for using dd-cfDNA as a biomarker in organ transplantation

Organ transplants are also genome transplants

→ **Possibility of serial, noninvasive monitoring for allograft injury**

De Vlaminck et al, Sci Transl Med 2014; 6: 241ra77

Graft cell death:
Release of nucleosomes into bloodstream

dd-cfDNA release reflects graft injury itself, i.e. the end-organ effects of the alloimmune response *

Nucleosomes:

DNA wound around histones
→ Released into the bloodstream as cfDNA

Causes of graft injury:

Rejection, ATN, ischemia, trauma, infection

Mechanisms of cfDNA release:

- **Necrosis >10,000 bp**
- **Apoptosis 60-200 bp**

Half-life in circulation:

- **~ 30 min – 2 hours**

** Whitlam JB et al, Am J Transplant 2019; 19: 1037-1049*

Oellerich M et al, Nat Rev Nephrol 2021; 17: 531-603
Sherwood K et al, J Immunol Meth 2018; 463: 27-38

Selected methods for dd-cfDNA determination

- **Droplet digital PCR using preselected SNPs**

  Beck, Clin Chem 2013
  Schütz, …, Oellerich, PLoS Med 2017
  Oellerich, Am J Transplant 2019

- **Next-generation shotgun or targeted sequencing (NGS)**

  Snyder, PNAS 2011
  De Vlaminck, Sci Transl Med 2014
  Grskovic, J Mol Diagn 2016
  Bloom, J Am Soc Nephrol 2017

- **PHABRE-PCR or INDEL qPCR**

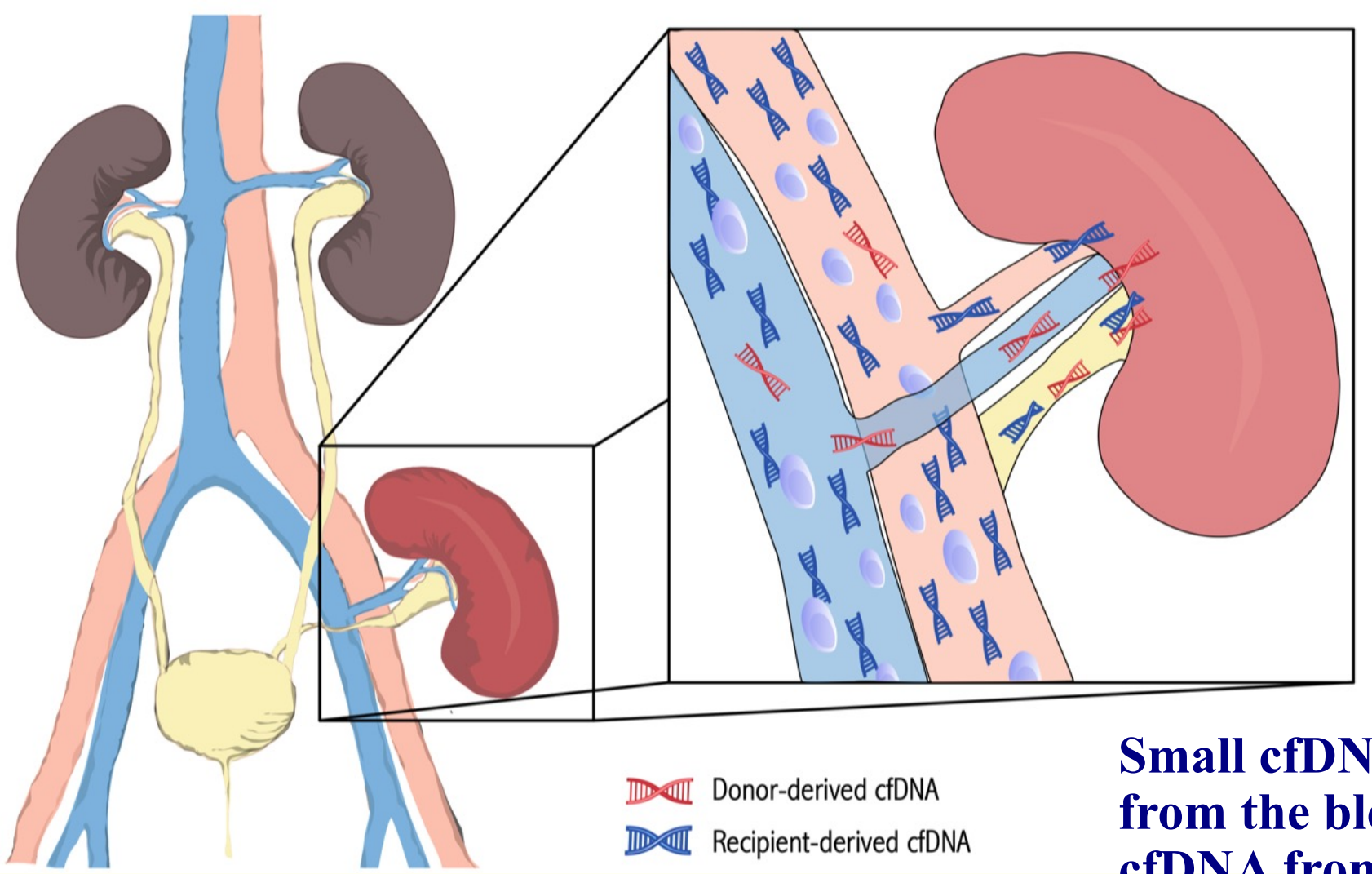
  Goh, Clin Chem 2017, Transplant direct 2019
  Dauber, Transpl Int 2019

Analytical validity of ddPCR and NGS methods to determine dd-cfDNA fraction

	Limit of blank (LoB) (%)	Limit of detection (LoD) (%)	Lower limit of quantification (LLoQ)	Linear quantifiable range (%)	Imprecision (CV) %
ddPCR	0.10	0.15	0.15	0.15 – 99.9	3 - 12
Targeted NGS	0.10	0.16	0.20	0.20 - 16	6.8
NGS	0.11	0.15	0.15	0.15 - 15	4.3

Data from *Oellerich M et al, JALM 2020; 5: 993-1004*

Origin of blood and urinary dd-cfDNA after KTx



Small cfDNA fragments from the blood and dd-cfDNA from the urinary tract appear in urine

Clinical validity of dd-cfDNA in transplantation - subset of 50 studies -

Reference	Patients	Reference	Patients
Lo The Lancet 1998	8 LTx 28 KTx	Whitlam Am J Transplant 2019	55 KTx
Snyder PNAS 2011	7 HTx	Huang Am J Transplant 2019	63 KTx
Beck Clin Chem 2013	17 LTx, 9 KTx, 8 HTx	Richmond J Heart Lung Transplant 2019	174 HTx
Oellerich Ther Drug Monit 2014	10 LTx	Gielis Nephrol Dial Transplant 2019	107 KTx
De Vlaminck PNAS 2015	51 LUTx	Sigdel J Clin Med 2019	193 KTx
Grskovic J Mol Diagn 2016	53 HTx	Khush Am J Transplant 2019	773 HTx
Schütz, …, Oellerich PLOS Medicine 2017	115 LTx	Oellerich Am J Transplant 2019	189 KTx
Bloom J Am Soc Nephrol 2017	102 KTx	Schütz, …, Oellerich Clin Chem 2020	303 KTx
Agbor-Enoh J Heart Lung Transplant 2018	157 LUTx	Agbor-Enoh Circulation 2021	169 HTx

Oellerich M et al, Nat Rev Nephrol 2021; 17: 591-603

Knight SR et al, Transplantation 2019;103: 273-283
Oellerich M et al, JALM 2020; 5:993-1004

Early detection of rejection after heart transplantation at an actionable stage

- **Lack of reliable non-invasive markers**
- **Endomyocardial biopsy (EMB) - current standard**

  Problems:
  - **sampling error**
  - **interobserver variability of interpretation**
  - **low sensitivity to detect early rejection**
  - **'biopsy-negative' rejection in ≤ 20% of HTx patients**
  - **uncommon (0.5-1.5%), but potentially serious complications (e.g. myocardial perforation)**

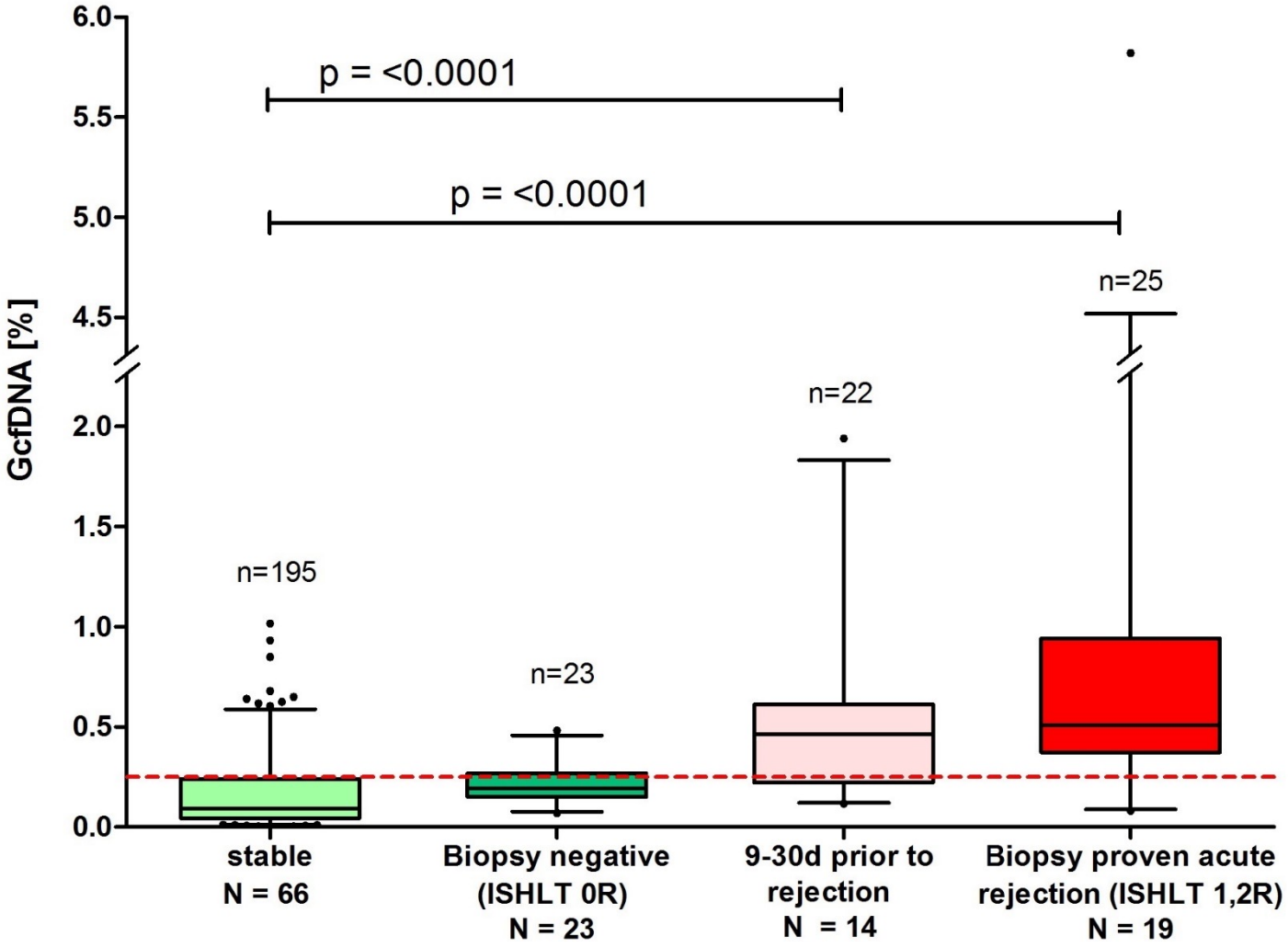
- **dd-cfDNA complements histology findings and allows comprehensive monitoring**

Agbor-Enoh S et al, Circulation 2021; 143: 1184-1197

Ahn KT et al, Transplant Proc 2015; 47: 504-510
Miller CA et al, Heart 2013; 99: 445-453

Beck J et al, Clin Chem 2013; 59: 1732-1741
Muñoz-Esparza C, Rev Esp Cardiol 2011; 64: 1109-1113

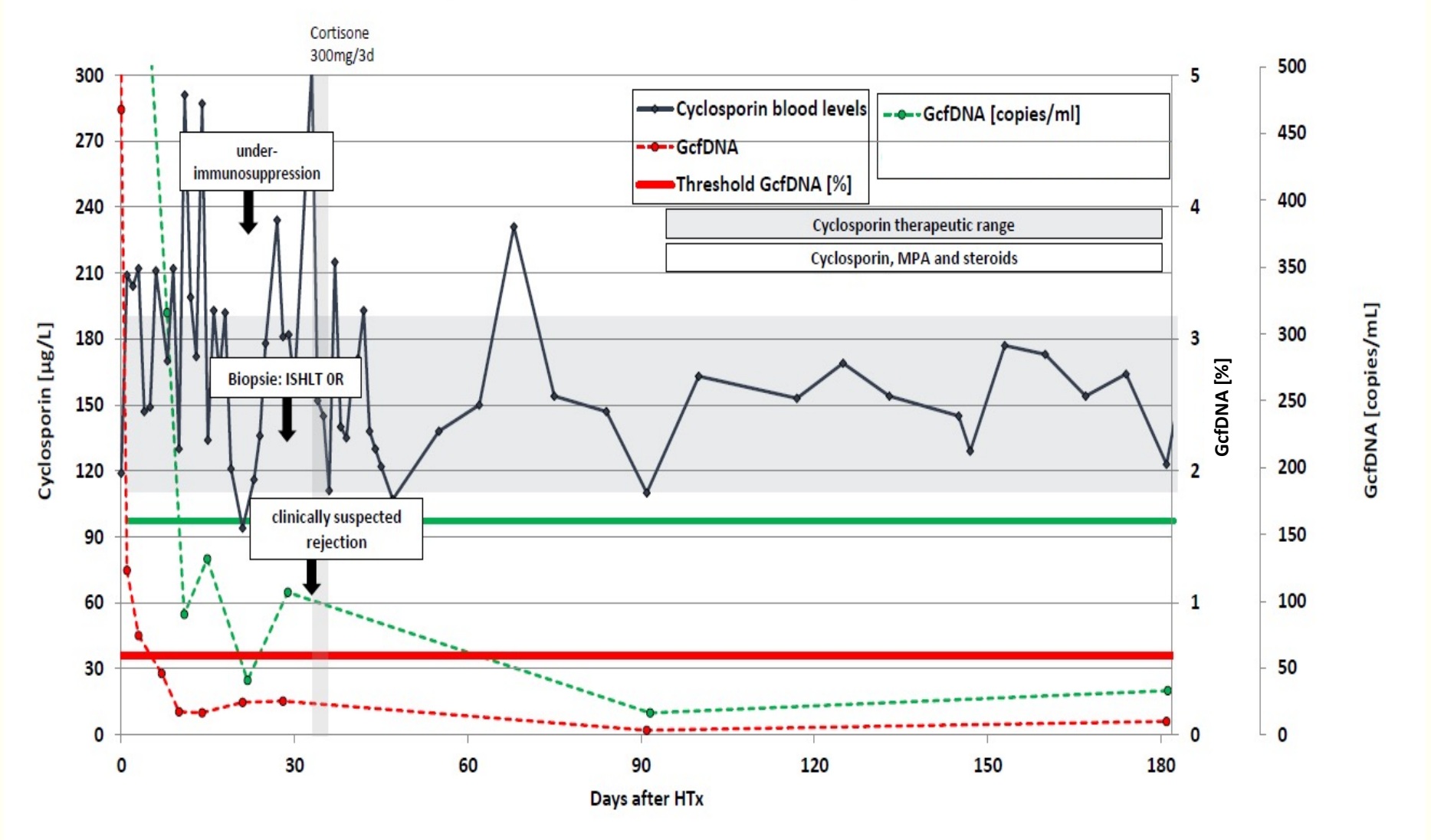
First year dd-cfDNA in stable HTx patients and during rejection episodes



Sensitivity: 76%
Specificity: 91%
PPV: 49%
NPV: 97%

Adapted from: Schütz E, …, Oellerich M.
69th AACC Annual Scientific Meeting Abstracts, 2017: S42-43

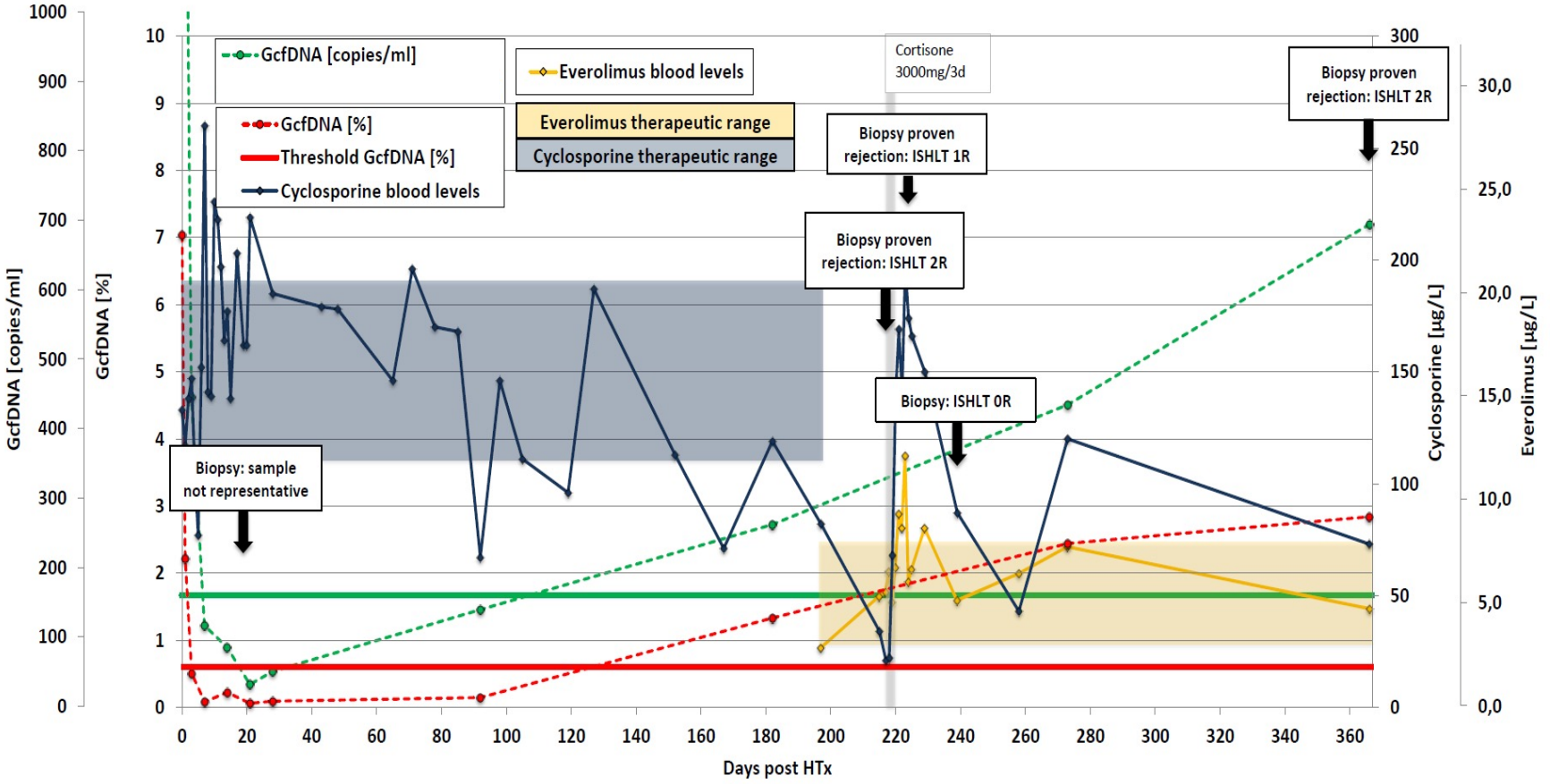
dd-cfDNA in a HTx recipient with clinically suspected rejection and negative biopsy



Schütz E, … Oellerich M. AACC Poster San Diego 2017

dd-cfDNA in a HTx recipient with late acute rejections

Serum creatinine	0,9	1	1,4	1,4	1,7	1,4	1,3
Days post HTx	10	21	28	92	182	273	366



Schütz E, … Oellerich M. AACC Poster San Diego 2017

% dd-cf DNA to detect heart allograft acute rejection

% dd-cf DNA in relation to acute rejection	
ABMR grade ≥ 2 N=15	1.68% (IQR, 0.49-2.7%)
ACR grade ≥ 2 N=38	0.34% (IQR, 0.28-0.72%)
ABMR	AUC-ROC 0.95
ACR	AUC-ROC 0.85

Cut-off: 0.25%

Data from: Agbor-Enoh et al, Circulation 2021; 143: 1184-1187

Detection of rejection by dd-cfDNA (%) in the first year after liver transplantation

Prospective multicenter trial using ddPCR

Histopathology findings	N	n	dd-cf DNA (%) Median (95% CI)
Biopsy proven acute rejection (BPAR)	17	31	29.6 (23.6 – 41.0)*
HCV^+ (rejection-free)	17	68	5.9 (4.4 – 10.3)
Stable Phase (rejection-free) (SP)	88	282	3.3 (2.9 – 3.7)

* $p < 0.001$ vs SP cut-off: 10% sensitivity: 90.3 % specificity: 92.9 %

AUC-ROC: dd-cfDNA: 97.1 %; AST: 95.7 %; ALT: 95.2%; γ-GT: 94.5 %; bilirubin: 82.6 %

dd-cfDNA superior to LFTs for BPAR detection

Data from Schütz E, et al PLOS Medicine 2017; 14: e1002286

dd-cfDNA in reference populations of KTx recipients

Oellerich[1]	0.29%* (IQR: 0.17-0.56%)
Bromberg[2]	0.21%* (IQR: 0.12-0.39%)
Bloom[3]	0.30%* (IQR: 0.14-0.77%)
Sigdel[4]	0.40%*
Gielis[5]	0.46** (± 0.21%)

* Median; ** Mean

Data from: [1]Am J Transplant 2019; [2]JALM 2017; [3]Am Soc Nephrol 2017; [4]J Clin Med 2019; [5]PLoS One 2018

Diagnosis of antibody-mediated rejection (ABMR) in KTx recipients

Donor-specific HLA antibody (DSA):

- Risk factor for ABMR and late graft loss
- Under-immunosuppression favors DSA development

ABMR:

- Associated with 20-30% allograft loss*
- Diagnostic options:
  - Histology: inflammation of vasculature
  - Immunopathologic findings: e.g. antibody-mediated injury of donor endothelium; C4d positivity; DSA
  - mRNA tissue-based gene signature (MMDx)

- dd-cfDNA useful for early ABMR detection (e.g. DSA$^+$ patients)
- Early detection of subclinical ABMR enables adapted therapeutic interventions and may improve outcome

Loupy A et al, JASN 2015; 26: 1721-1731 *Halloran et al, AmJ Transplant 2019* **Kim M et al, Pharmacotherapy 2014; 34: 733-744.*
Parajuli S et al, Transplantation 2019 *Hoshino J et al, Transplantation 2012; 93: 1173-1178*

dd-cfDNA monitoring may decrease risk for late graft loss in KTx patients

dd-cfDNA has potential to identify unrecognized under-immunosuppression in KTx patients at risk of dnDSA formation and chronic antibody-mediated rejection.

(e.g. in recipients with high epitope mismatch burden, high immune competence, or non-compliance)

Oellerich, M et al, Nat Rev Nephrol 2021; 17: 591-603

dd-cfDNA(%) in ABMR and TCMR

KTx multicenter study (DART) using targeted NGS (AlloSure®)

Histopathology findings	n	dd-cfDNA (%)
Chronic, active ABMR	10	2.2 (IQR, 1.0-4.1)
Acute, active ABMR	6	3.7 (IQR, 1.4-6.1)
TCMR - I A - ≥ I B	11 5 6	0.22 (IQR, 0.17-1.57) 0.2 1.2
No active rejection	71	0.3 (IQR, 0.14-0.77)

Sensitivity: 59%
Specificity: 85%

Diagnostic accuracy: 74%
Cut-off: 1.0%

PPV: 61%
NPV: 84%

Data from: Bloom RD et al, J Am Soc Nephrol 2017; 28: 2221-2232

dd-cfDNA(%) in KTx patients with TCMR or ABMR

Prospective single-center study using targeted NGS* (AlloSure®)

Histopathology findings	dd-cfDNA %		
	median	IQR	p
No rejection (n=29)	0.38 %	0.26% – 1.10 %	
TCMR (n=10)	0.27 %	0.19% – 1.30%	< 0.01
ABMR (n=22) ABMR/TCMR (n=2)	1.40 %	1.15% – 2.60%	<0.001

Sensitivity: 79% Specificity: 72% PPV: 77% NPV: 75%
Diagnostic accuracy: 71% Cut-off: 0.74%

False negative TCMR results:

- **Presumably insufficient detection of short fragments due to use of relatively long amplicons (100-130 bp) in the employed test**
- **TCMR marked by interstitial inflammation and tubulitis potentially causing more extensive dd-cfDNA fragment degradation**

Data from Huang E et al, Am J Transplant 2019; 19: 1663-1670 **Grskovic M et al, J Mol Diagn. 2016; 18: 890-902*

Amplicon size related to amount of dd-cfDNA(%) determined by INDEL qPCR

KTx patients	Short PCR* dd-cfDNA (%) Median	Long PCR** dd-cfDNA(%) Median
Acute rejection (N=8)	5.24	1.48
No rejection (N=12)	1.50	0.76
Borderline rejection (N=9)	1.91	1.20

* Short PCR, amplicon size: 86-128 bp

**Long PCR, amplicon size: 106-156 bp

Smaller size amplicons preferable to quantify dd-cfDNA

Data from Dauber EM et al, Transpl Int 2019; doi: 10.1111/tri.13554

dd-cfDNA(%) in KTx patients with ABMR and TCMR

Methodology: mmPCR NGS

Histopathology findings	dd-cfDNA %		
	n	Median	Range
ABMR	16	2.22*	0.12 – 23.9
ABMR/TCMR	12	2.56*	0.09 – 8.8
TCMR **	10	2.69*	1.01 – 9.77
No rejection	82	0.4	0.03 – 6.8

Cut-off: 1.0%

***No significant difference between rejection groups (p=0.855)**

**** t score >2, i score >2**

Data from: Sigdel TK et al, J Clin Med 2019; 8, 19. doi:10.3390/jcm8010019

Diagnostic performance of dd-cfDNA and eGFR for detection of acute rejection in KTx patients

	dd-cfDNA	eGFR
AUC - ROC	0.87	0.74
Sensitivity	88.7%	67.7%
Specificity	72.6%	65.3%
PPV	51.9%	39.4%
NPV	95.1%	85.9%
Cut-off	1.0%	<60ml/min/1.73 m^2

Data from: Sigdel TK et al, J Clin Med 2019; 8, 19. doi:10.3390/jcm8010019

Absolute dd-cfDNA quantification by ddPCR

Absolute quantification of dd-cfDNA (cp/mL) has the advantage that it is not affected by changes in recipient cfDNA (e.g. by infection, exercise).

~ 90% of cfDNA in recipient plasma stems from white blood cells undergoing natural apoptosis.

Calculation of dd-cfDNA concentration (cp/mL):

total cfDNA (cp/mL) x dd-cfDNA %

(cfDNA extraction and ddPCR amplification efficiency must be considered)

Oellerich M et al, Am J Transplant 2019; 19: 3087-3099

Detection of rejection by absolute dd-cfDNA quantification in the first year post-KTx

Prospective single center trial using ddPCR

Histopathology findings	N	n	dd-cf DNA (cp/ml) Median (IQR)
Biopsy proven acute rejection (TCMR, ABMR)	15	22	82 (53 – 147)*
ATN	29	31	64 (43 – 126) **
IF / TA	24	30	35 (23 – 84) ***
Stable Phase (rejection-free) (SP)	83	408	25 (11 – 60)

* $p < 0.0001$ vs SP ** $p = 0.0001$ vs SP *** $p = 0.02$ vs SP

Cut-off: 50 cp/ml; sensitivity: 73 %; specificity: 73 %; NPV: 98 %

AUC-ROC: 83 % dd-cfDNA (cp/ml); 73 % dd-cfDNA (%)

Data from: Oellerich M, et al AmJ Transplant 2019; 19:3087-3099

Urinary dd-cfDNA as a marker of kidney transplant injury

Patients[1)]	N 63	dd-cfDNA ChrY copies/µg creat
Stable graft (STA)	41	2.4 ± 3.3
Chronic allograft injury (CAI)[2]	10	2.4 ± 2.4
Acute rejection (TCMR)	8	20.5 ± 13.9*
BK virus nephropathy (BKVN)	4	20.3 ± 15.7*

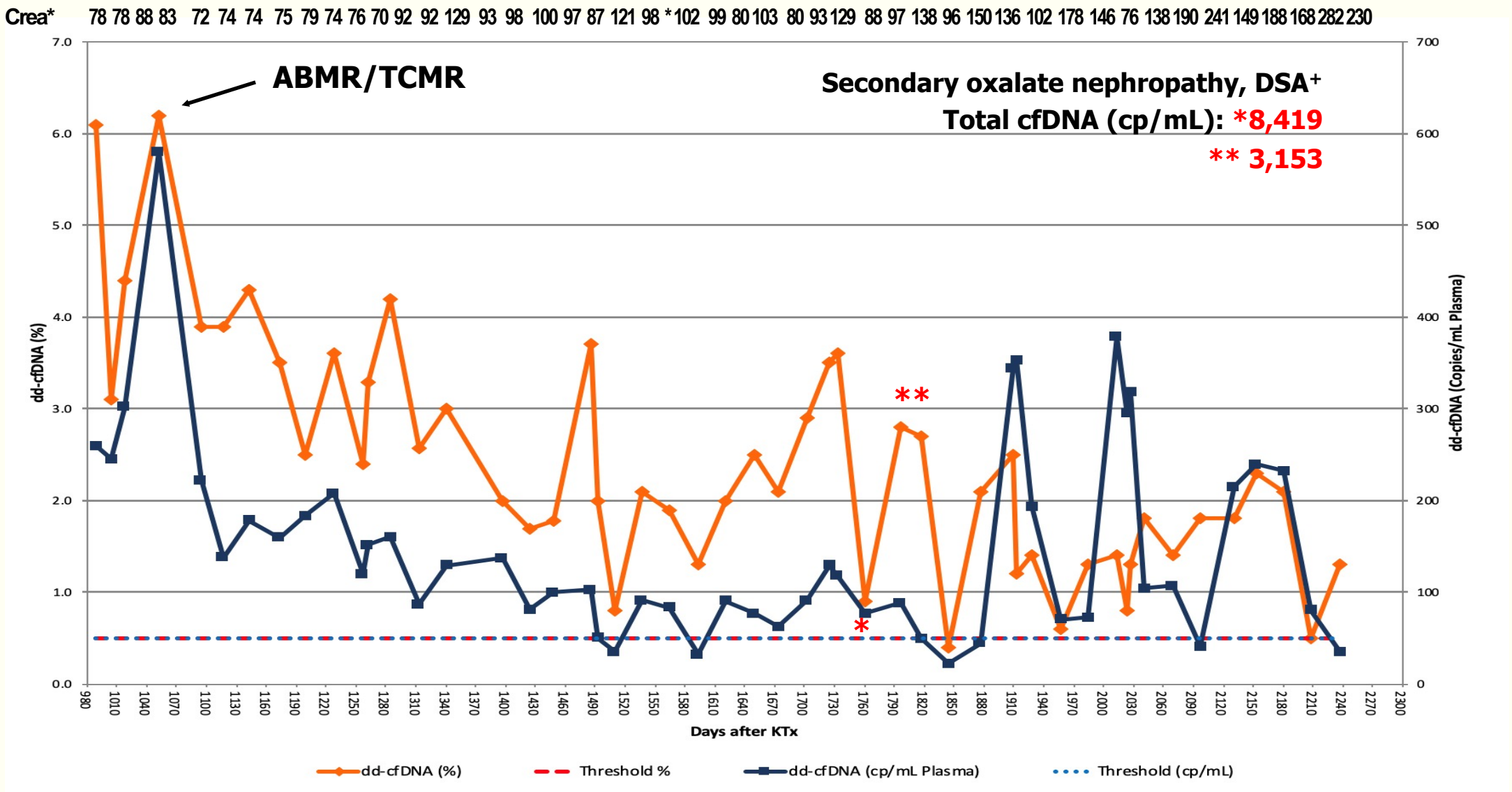
*$p \leq 0.001$ vs STA and CAI [1)]Female recipients of male donors

[2)]CAI: tubular atrophy score ≥1 and interstitial fibrosis score ≥1

→ Limitation: no increase with advanced interstitial fibrosis

Data from: Sigdel TK et al, Transplantation 2013; 96: 97-101

dd-cfDNA fraction (%) and absolute quantification in an adolescent patient 3 to 6 years after KTx



Reference range: 40-68 (-105) µmol/L

Beringer O, Beck J, … Oellerich M, unpublished

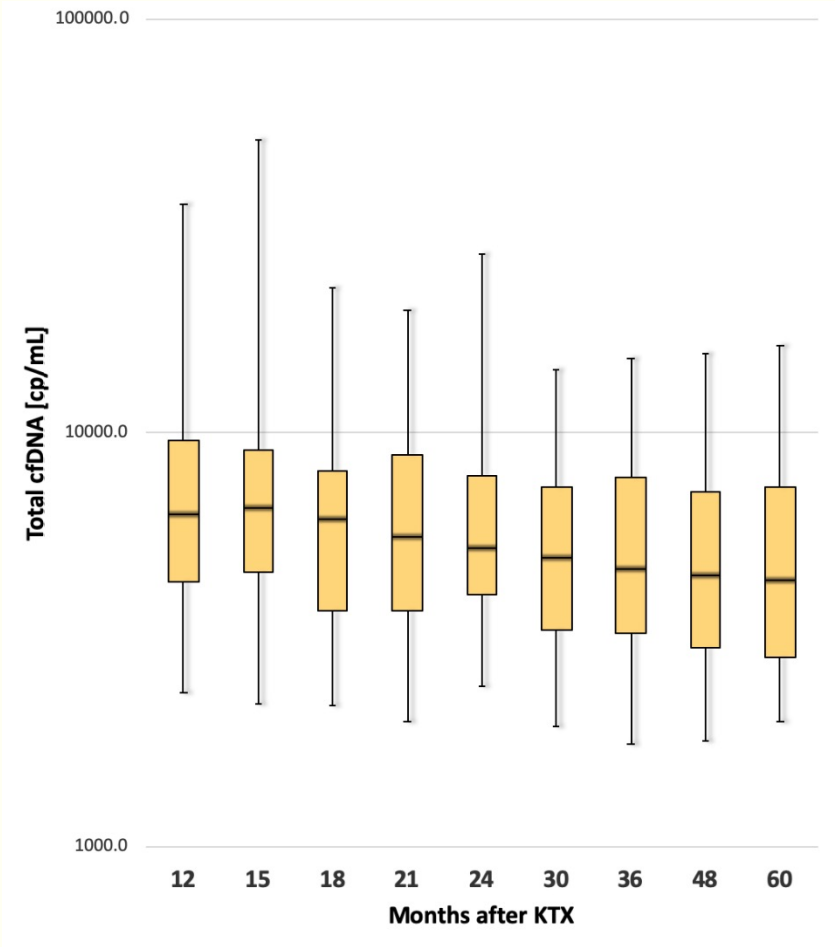
Variability of recipient and total cfDNA plasma levels in KTx

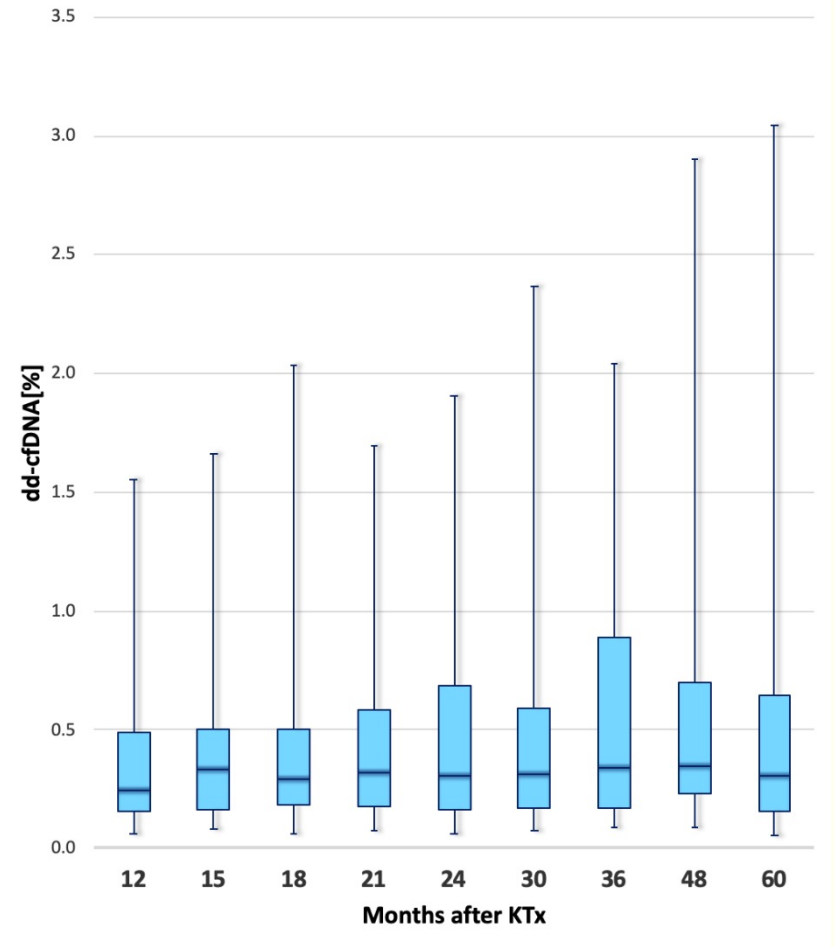
- **Recipient cfDNA (median):**
  - 1st year post-transplant: 6370 cp/ml
  - 5 years post-transplant: 4480 cp/ml
- **Total cfDNA:**
  - Increase due to inflammatory illness:
    - E. coli bacteremia 20542 cp/ml
    - Hemoptysis 19651 cp/ml
  - Decrease due to leukopenia: 1559 cp/ml

Leukopenia and leukocytosis can alter dd-cfDNA fraction as recipient cfDNA accounts for the major part of the denominator in fractional quantification. Absolute quantification is not affected.

Oellerich et al, Nat Rev Nephrol 2021; 17: 591-603
Whitlam et al, Am J Transplant 2019; 19: 1037-1049
Schütz et al, Clin Chem 2020; 66: 1290-1299
Osmanodja B. et al, Transplant Direct 2021; accepted

Increased dd-cfDNA(%) due to a decrease of total cfDNA during long-term surveillance





In contrast to fractional dd-cfDNA(%) the threshold for absolute quantification (cp/mL) was not affected during long-term treatment.

Data from: Schütz E. et al. Clin Chem 2020; 66:1290-1299

Dynamics of cfDNA in the first 5 years of KTx

- **Decline of total cfDNA with time after KTx presumably due to a decrease in apoptosis rate for white blood cells as immunosuppressant drug doses are tapered off**
- **CNI seem to have a negative effect on cell stability**

Schütz E. et al., Clin Chem 2020; 66: 1290–1299
De Vlaminck et al., Clin Chem 2020; 66: 1257–1258

Advantages of targeted ddPCR based testing for dd-cfDNA (TheraSure)

- Absolute quantification in addition to fractional determination (not affected by changes in recipient cfDNA, threshold not affected during long-term treatment)
- Detection of TCMR and ABMR
- Monitoring of donor lymphocyte macrochimerism in LTx patients with GVHD (adapted ddPCR assay)
- Short turnaround time (1 (-2) days)
- Reasonable cost (useful for serial determination)

Oellerich, M. et al, Nat Rev Nephrol 2021; 17: 591-603

Schütz, E. et al; PLOS Medicine 2017; 14: e10022810

Development of clinical practice recommendations regarding monitoring frequency

Proposed sampling schedule for dd-cfDNA

- One and two weeks after transplantation
- Monthly for 6 months
- Every 3 months thereafter
- In case of suspected graft damage
- 7-10 days after immunosuppressant dosage changes
- No testing within 12 h after tissue biopsy

Oellerich M et al, Nat Rev Nephrol 2021: 17: 591-603

Management costs of kidney transplant patients in the first year

Functioning kidney transplant	**19,364 $**
Failure with return to dialysis	**75,836 $**
Failure, with re-transplant	**111,891 $**
Kidney biopsy (comprehensive costs)	**3,931 $**

Puttarajappa CM, Am J Transplant 2021;21: 186-196

First MR, J Health Med Econ 2017; 3, No. 1:3;
Oellerich M et al, JALM 2020; 5:993-1004

Stakeholders involved in delivering and receiving care in transplantation

- **Transplant patients** whose care could be altered by the less invasive graft injury detection
- **Clinicians** who manage solid organ transplant patients
- **Laboratory medicine specialists** who analyze and interpret test results
- **Hospital management, insurance companies / public payers, policy makers** who are involved in providing value-based health care (value: outcomes relative to costs)

Oellerich M et al, JALM 2020; 5: 993-1004

Benefits of dd-cfDNA testing in relation to outcome in transplantation

Patients:

- Detection or exclusion of graft injury or rejection
- Earlier transplant injury intervention
- Biopsy alternative
- Early diagnosis of subclinical antibody-mediated rejection
- Detection of under-immunosuppression
- Evaluation of infectious complications of kidney allograft
- Personalized immunosuppression

Oellerich M et al, JALM 2020; 5: 993-1004

Benefits of dd-cfDNA testing in relation to outcome in transplantation

Transplant physicians:

- Better personalized immunosuppression guidance (e.g. during tapering)
- Enhanced biopsy interpretation
- Less trial and error changing of immunosuppression
- Less time dealing with complications
- Indication of response to rejection treatment

Laboratory medicine specialist:

- Increased involvement in molecular diagnostics regarding use and interpretation of tests

Hospital management, insurance companies/public payers, policy makers

- Expected cost savings due to a decreased burden for care-givers (e.g. due to fewer retransplantations or return to dialysis in KTx)

Oellerich M et al, JALM 2020; 5: 993-1004

Diagnostic performance of dd-cfDNA for detection of acute rejection – pooled data from published studies

	AUC–ROC		Sensitivity		Specificity		PPV		NPV	
		N	%	N	%	N	%	N	%	N
KTx *	0.81 (0.71-0.91)	8	79 (59-89)	8	76 (69-85)	8	47 (12-77)	8	92 (75-98)	8
HTx **	0.81 (0.69-0.92)	5	66 (54-81)	5	86 (76-93)	5	36 (12-80)	4	93 (81-99)	4

N = number of studies; mean value (range)

**Oellerich M et al, Am J Transplant 2019*
**Huang E et al, Am J Transplant 2019*
**Whitlam JB et al, Am J Transplant 2019*
**Sigdel TK et al, J Clin Med 2019*
**Dauber EM et al, Transpl Int 2019*
**Bloom RD et al, J Am Soc Nephrol 2017*

***Agbor-Enoh et al, Circulation 2021*
***Knüttgen et al, Transplantation 2021*
***De Vlaminck et al, Sci Transl Med 2014*
***Richmond ME et al, J Heart Lung Transplant 2019*
***Khush KK et al, Am J Transplant 2019*

dd-cfDNA as a marker of graft injury - where are we now?

Clinical validity:

- detects rejection early at an actionable stage
- reflects the severity of graft injury
- useful to exclude graft injury
- complements histology findings
- helps avoid unnecessary biopsies
- indicates response to rejection treatment
- detects under-immunosuppression

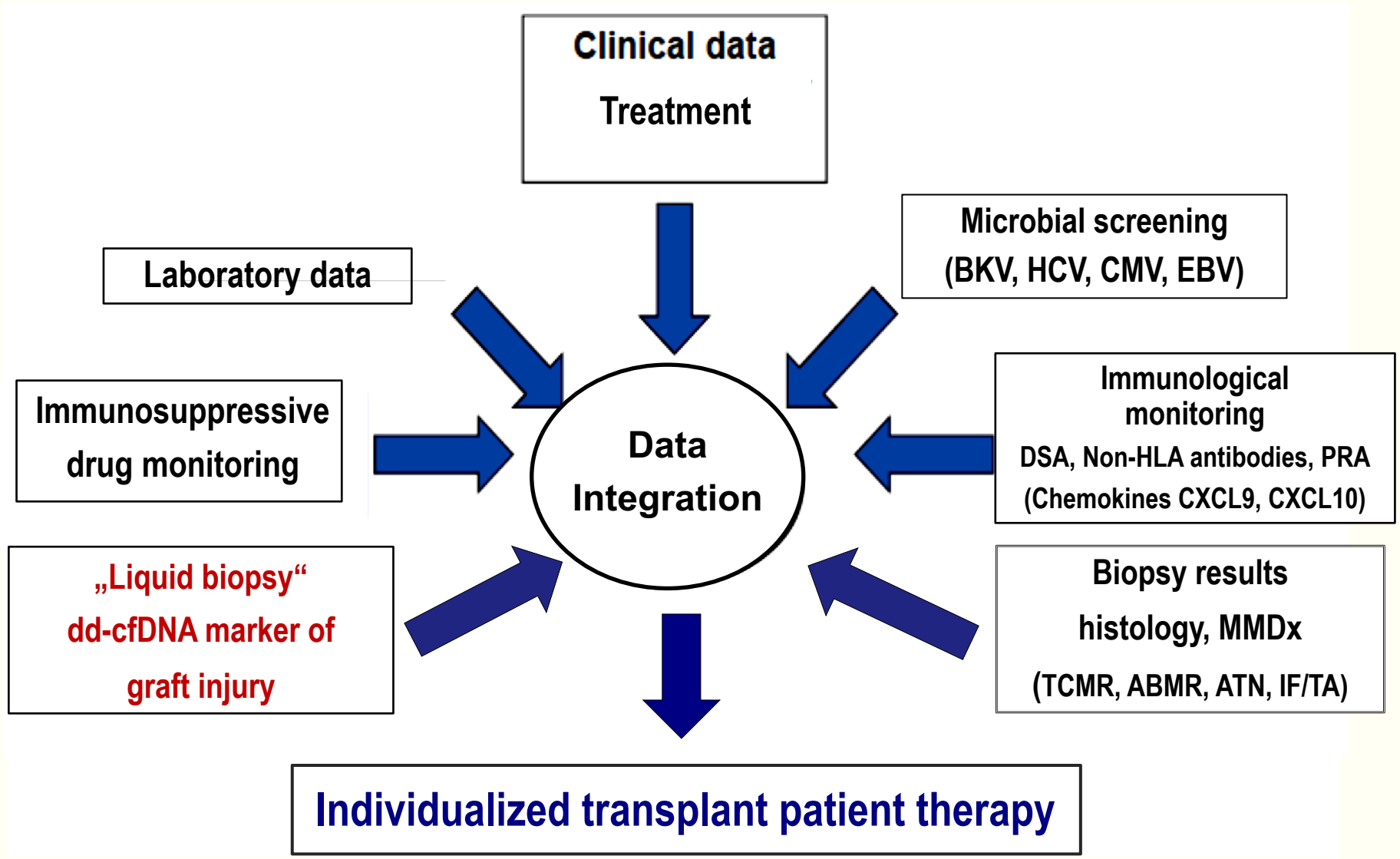
Facilitates personalized immunosuppression
→ Shifts emphasis from reaction to prevention

Coverage for dd-cfDNA routine testing by Medicare

Oellerich M et al, Nat Rev Nephrol 2021; 17: 591-603

Knight SR et al, Transplantation 2019;103: 273–283

Personalized immunosuppression to reduce premature graft loss



Adapted from: Alex J Rai, PhD; Columbia University Medical Center, New York; pers. commun. 2018

Thank you

Personalized Diagnostics Gains Ground in Transplantation - Challenges Remain

Sagarmatha, March 12, 2013

Ekkehard Schuetz, MD, PhD, FAACC
SVP, Therapeutic Monitoring R&D at Oncocyte

Dr. Schuetz has over 30 years of experience in laboratory diagnostics with a focus on molecular diagnostics in transplantation and has spent over 20 years conducting cell-free DNA research. Dr. Schuetz has 200 scientific publications as well as numerous patents. Additionally, he is the inventor of digital PCR technology used to quantify donor-derived cfDNA for early detection or rejection.

Transplant

TheraSure™ Transplant-MONITOR

Prof. Ekkehard Schütz, FAACC – Sr. VP Blood based Monitoring

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Where Tomorrow LIVES

Sept. 21, 2021

Any statements that are not historical fact (including, but not limited to statements that contain words such as "will," "believes," "plans," "anticipates," "expects," "estimates" and similar expressions) are forward-looking statements. These statements include those pertaining to the time to complete and the results of OncoCyte's ongoing CLIA Validation study of DETERMA™, the closing of our planned acquisition of Razor and the Razor Test, implementation and results of research, development, clinical trials and studies, commercialization plans, future financial and/or operating results, and future opportunities for OncoCyte, along with other statements about the future expectations, beliefs, goals, plans, or prospects expressed by management. Forward-looking statements involve risks and uncertainties, including, without limitation, risks inherent in the development and/or commercialization of potential diagnostic tests or products, uncertainty in the results of clinical trials or regulatory approvals, the capacity of our third-party supplied blood sample analytic system to provide consistent and precise analytic results on a commercial scale, the need and ability to obtain future capital, maintenance of intellectual property rights, and the need to obtain third party reimbursement for patients' use of any diagnostic tests we commercialize. Actual results may differ materially from the results anticipated in these forward-looking statements and accordingly such statements should be evaluated together with the many uncertainties that affect the business of OncoCyte, particularly those mentioned in the "Risk Factors" and other cautionary statements found in OncoCyte's Securities and Exchange Commission filings, which are available from the SEC's website. You are cautioned not to place undue reliance on forward-looking statements, which speak only as of the date on which they were made. OncoCyte undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made, except as required by law.

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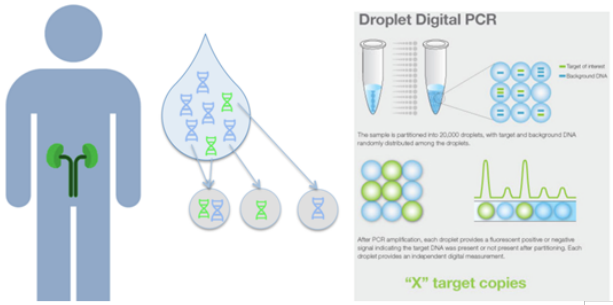
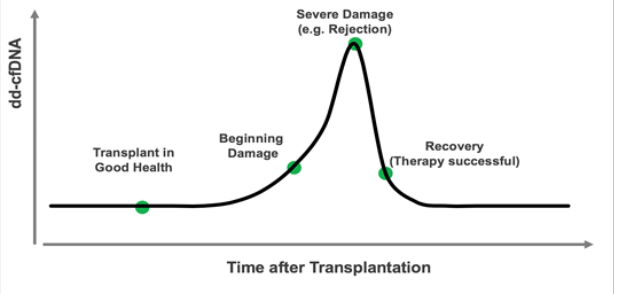
TheraSure™ Transplant MONITOR





Multiple Clinical Validation studies show that Rejection is associated with increased release of Graft DNA (donor derived cfDNA – "dd-cfDNA") into blood stream

Measurement using graft (donor)-specific assays in droplet digital PCR

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Design Goals

Fast to provide Actionable results

Scalable for high throughout

Cost effective for life-time surveillance

LOQ sufficient for medical needs

- Limited high MAF SNP-panel (PCR)
- BioRad ddPCR as read-out device

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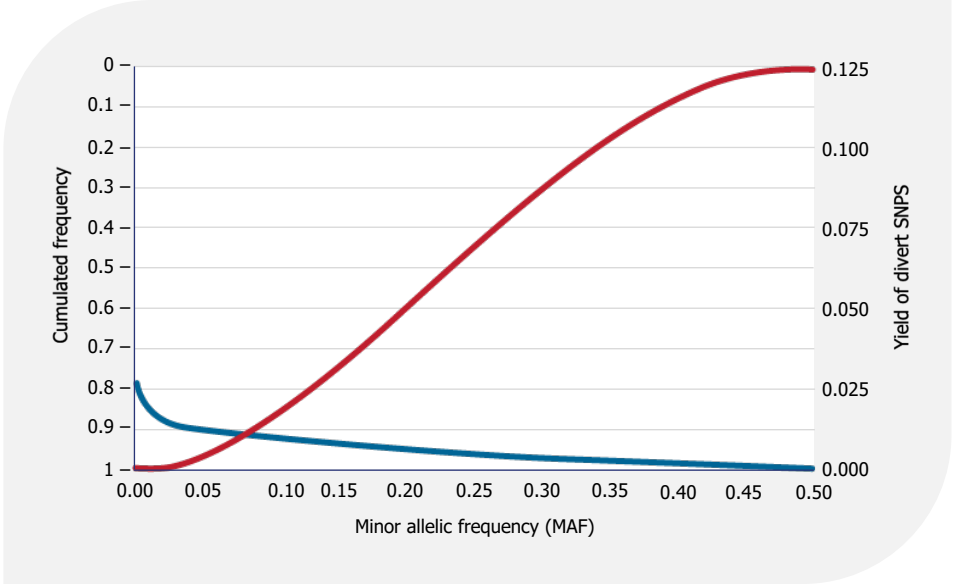
Older Technologies vs. our Approach

- First description of dd-cfDNA by Lo YM, et al. Lancet. 1998;351(9112):1329-30
- Older technology: Snyder et al. using mass sequencing after donor genotyping in 2011
  - SNP assay of donor and recipient to detect SNPs were recipient and donor differ
  - Mass sequencing of recipient plasma and count number of reads from donor
  - Only approx. 10,000 of 30mllion reads are useful, of which about 20 are donor derived (0.7 ppm)!
  - 99.999% of reads are waste!
  - Extremely time consuming and highly costly technology
- Our Technology: Beck et al. using targeted approach with digital PCR in 2013
  - Using SNP loci that are known to be highly heterogeneous in the human population (high minor allelic population frequency) in digital PCR
  - Statistical chance to be different between donor and recipient is 12.5% (AA vs. BB) and 25% (AA or BB vs. AB)
  - 37.5% of selected targets are informative (compared to ~ 1 in a million in older assays!!)
  - No need to have genetic material from the donor (huge problem for old assays)
  - Added absolute quantification in 2015 (IP-protected dPCR technique)
  - Extremely fast turnaround time and reasonable costs

Transplant Using Genomics for Assay Development



New Approach: using known SNPs that differentiate the graft from host to quantify graft cell-free DNA in blood samples "liquid biopsy"

Beck J et al. *Digital Droplet PCR for Rapid Quantification of Donor DNA in the Circulation of Transplant Recipients as a Potential Universal Biomarker of Graft Injury.* Clin Chem 2013; 59 1732-41.

IP protection in US and EU

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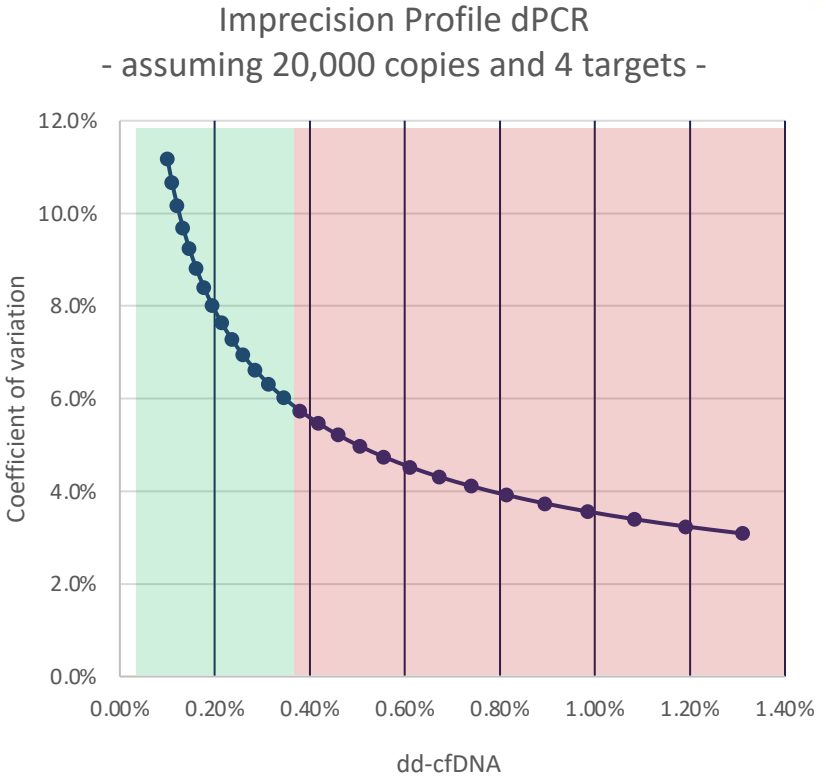
Digital PCR

- Next level of precision for quantification
- Basic principle described >10y ago
  - Dilution of sample
  - Partitioning into numerous containers
  - Single PCRs with average 1 template
  - Counting of positive PCR reactions
  - Calculation of concentration from Poisson distribution
- No need for quantitation standards; primarily quantitative
- Intrinsic precision assessment: SD=√N



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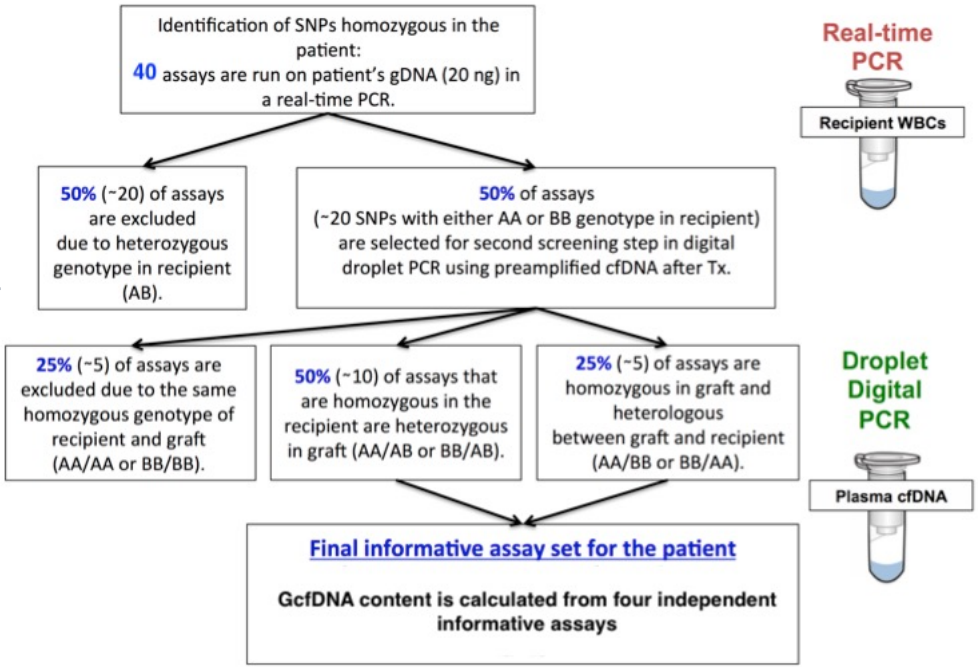
TheraSure™ Method Overview

For patients <u>not known</u> yet, the first step is to define the informative SNPs

- Simple workflow to be done only <u>once per patient</u>



Acc. to: Beck J, et al. ***Digital Droplet PCR for Rapid Quantification of Donor DNA in the Circulation of Transplant Recipients as a Potential Universal Biomarker of Graft Injury.*** Clin Chem 2013; 59 1732-41

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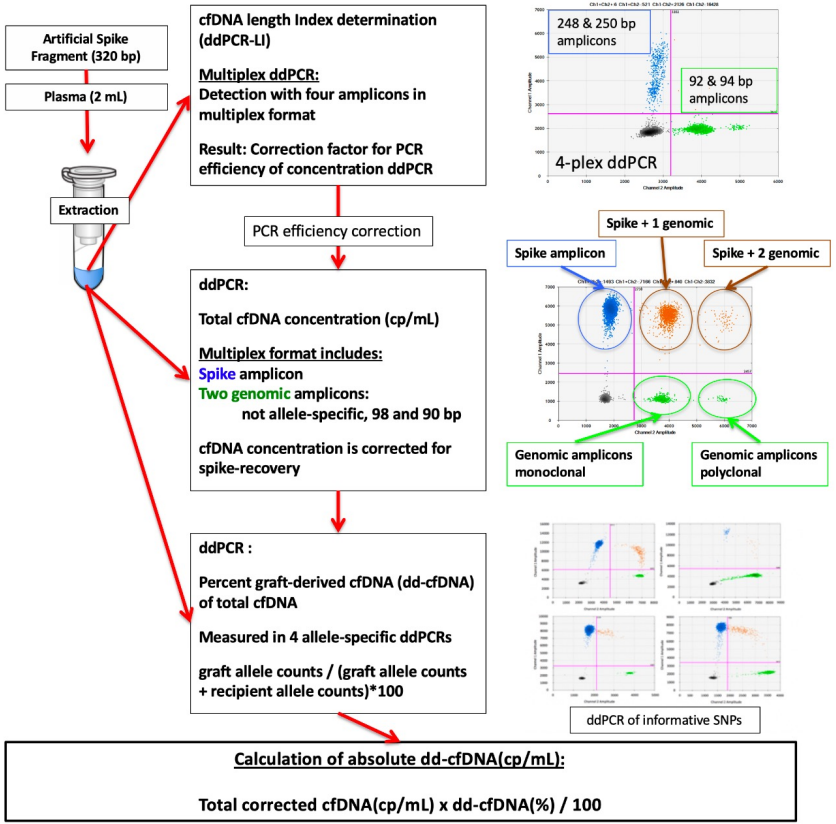
TheraSure™ Transplant dd-cfDNA Quantification

For each sample dd-cfDNA will be quantified acc. to this workflow



Multiplex ddPCR (1)
- 4 target amplicons
- assessing fragmentation

Multiplex ddPCR (2)
- 3 targets (probes)
- assessing extraction efficacy
- quantifying total cfDNA

Singleplex ddPCRs (3)
- 4 different ddPCRs
- 2 alleles (probes) each
- percentage dd-cfDNA quantified

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The Hypothesis of absolute dd-cfDNA Values

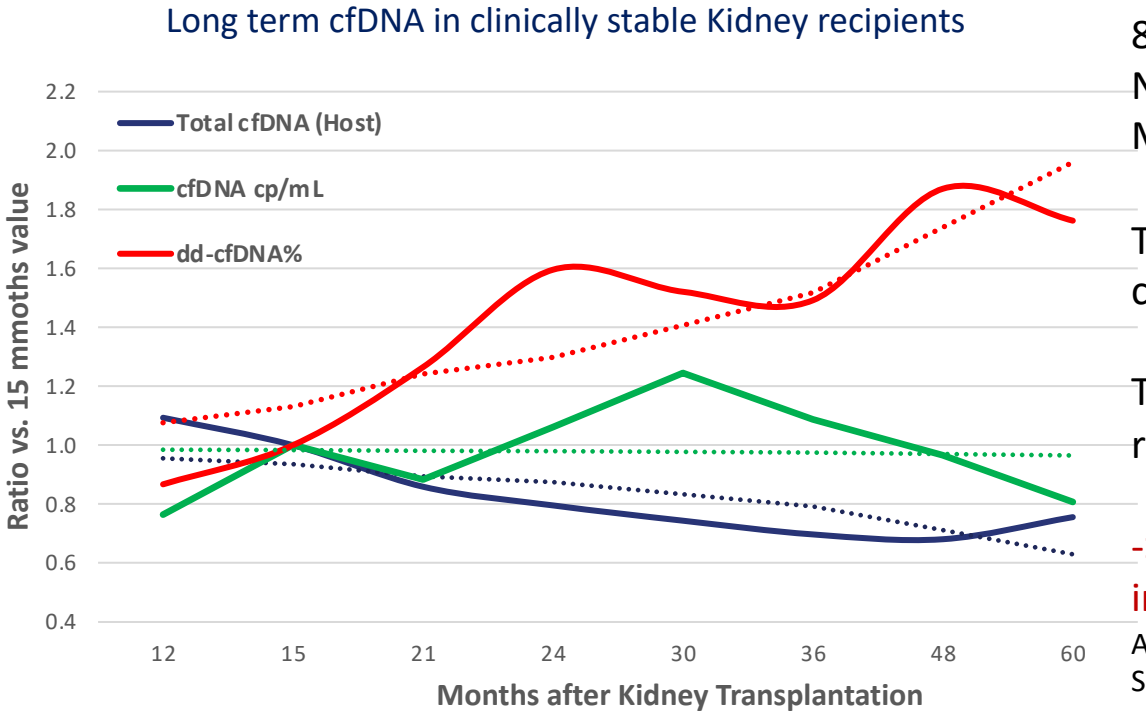
Donor-derived cfDNA percent has confounding variables

- Changes in host cfDNA (the denominator – mainly from leukocytes) will change dd-cfDNA percentage without pointing to the transplant cfDNA true concentration
- Numerous physiological and pathophysiological conditions resulting in changes – well published: e.g. exercise, stress, infections, drugs
- dd-cfDNA percent can therefor change at the same true concentration in mL of plasma
- Can (and will) lead to clinically misleading results of percentage

The tapering of immunosuppressants (ISD) after Transplantation

- Is done to ameliorate the side effects of ISDs
- Should lead to a decreased host total cfDNA (based on pharmacology), which represents the denominator of percentage calculations
- Should be observable in stable organ recipients

Study result:
Up crawling dd-cfDNA percentage over time in clinically healthy patients with unchanged true concentration



85th percentile shown
N=303 patients (72-135/time point)
Mainly under Tacrolimus

Total cfDNA and dd% highly inverse correlated (R^2=0.87,p<0.0001)

True concentration of dd-cfDNA remains stable

-> FALSELY elevated dd-cfDNA% values in long term patients!

Acc. to:
Schütz E et al. Clin. Chem. 2020;66(10):1290-9

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TheraSure™ Technology Competition Advantage

ddPCR and NGS technologies for quantification of circulating graft (donor) derived cfDNA in the plasma of organ recipients compared

dd-cfDNA Assay	Absolute values	Lower Limit of quantification	Upper Limit of quantification	Imprecision (CV)	Turnaround Time
Chronix (ddPCR)	Yes [a]	0.15%	99.9%	3 – 12 %	1 day
CareDx (NGS) [c]	No	0.20%	16.0% [b]	6.8%	2-3 days
Natera (NGS) [c]	No	0.15%/0.29%	15.0% [b]	2-5%	4 days(min)

[a] Superior for detection of Kidney rejection (AUC=.83 vs .73 for percentage)

[b] Can't be used in Liver recipients, since dd-cfDNA values are far greater than 16%

Cave: *a recent publication show that* ***also in Kidney values of 30% occur!*** *(Gielis et al. 2019 doi:10.1093/ndt/gfz091)*

[c] Data as published by competitors

(Note: Natera claims wider linear range than CareDx, but reported only up to 15%)

- **Cost of Goods for Chronix's TheraSure™ Tx are only a fraction of NGS techniques**
- **Fast turnaround accommodates clinical needs and demands**

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TheraSure™ Transplant MONITOR

- Scientific Track Record -

Chronix TheraSure Transplant MONITOR is validated in large clinical studies with:

119 Liver recipients (PLOS Med. ‘17)
345 Kidney recipients (Am J Transplant ’19; Clin Chem ‘20)
87 Heart recipients (Transplantation ‘21)

- >20 own publications and congress contributions in peer reviewed scientific journals
- Several scientific awards
- >100 citations in peer reviewed articles
- >60 total publications on the use of dd-cfDNA as tool for Transplant Monitoring in the medical literature

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TheraSure™ Summary

Validated in Clinical Studies on ~600 patients and >5,000 samples from Kidney, Heart and Liver Recipients

Clinical Study	Sensitivity	Specificity	Neg PV	Pos PV
Liver (115pt)	90%	93%	99%	58%
Heart (83pt)	76% (75%*)	91% (96%*)	97% (97%*)	54% (73%*)
Kidney (189pt)†	73%	73% (92%*)	95% (96%*)	27% (55%*)

*When samples **without** any biopsy proven pathologies are used as comparators instead of "Clinically stable" ; predictive values calculated at prevalence of 12%. † Data for absolute dd-cfDNA as copies/mL plasma, dd-cfDNA percentage shows lower accuracy (AUC 0.83 vs. 0.73, p=0.02)

With **exceptionally high negative predictive values (PV)** for rejection the **Chronix TheraSure™ Transplant MONITOR** can **avoid unnecessary biopsies** in about 30% of cases

- Reduction of treatment costs
- Reduction of harm for the patient

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Transplant IP cfDNA

Title	Jurisdiction	Status	Priority	Patent Numbers	Description	Remarks
DETECTION AND QUANTIFICATION OF DONOR CELL-FREE DNA IN THE CIRCULATION OF ORGAN TRANSPLANT RECIPIENTS	EPO USPTO	Granted Allowed	29-May-13	EP3004388 TBA	Is covering the quantification of donor-derived cell-free DNA in transplantation using known SNPs with high MAF in the human population without knowledge of the donor genome.	The significance is that some other players are using the same principle and might infringe our IP
METHODS OF QUANTIFYING CELL-FREE DNA	EPO USPTO	Granted Granted	01-Oct-14	EP3201361 US10570443	Is describing and covering a method to reliably quantify any given cfDNA in a patient (Cancer and Tranplant). The significance is that the method can reliably quantify cfDNA independently of how much it is shortened, which takes place to very various extend in clinical situations (e.g. immuno- or chemotherapy).	The significance is that without this the values will be incorrect. Several companies could be interested to license this for improvement of their own assays in transplantation as well as cancer.

TheraSure™ Value Proposition KTx

The Value Proposition indicates that:

- dd-cfDNA monitoring can facilitate personalized immunosuppression and thereby potentially decrease premature graft loss.
- A major advantage is the detection of injury before clinical manifestation, which allows treatment of acute rejection and other causes of graft injury that have the potential to improve outcome.
- During immunosuppression minimization, dd-cfDNA is helpful to detect under-immunosuppression in patients at risk of de novo DSA formation.
- On a broader scale, dd-cfDNA monitoring has the potential to change clinical practice, save costs, and improve the management of transplant patients.

From: Oellerich, M. et al. Donor-derived cell-free DNA testing in solid organ transplantation: A Value Proposition. J. Appl. Lab. Med. 2020
Preprint at: https://academic.oup.com/jalm/advance-article/doi/10.1093/jalm/jfaa062/5843502

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Thank You

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eschuetz@oncocyte.com