Global Innovations in Patient Centered Kidney Care

Transplant Precision Medicine: the potential of measuring kidney function and fluid status

May 22, 2019

School of Medicine
& Health Sciences
THE GEORGE WASHINGTON UNIVERSITY

Carmel Indiana
Privately Held
Developing discoveries out of
Indiana University School of Medicine

First in Class Technology

The first clinically-viable direct and accurate measurement of Kidney Function (mGFR) and Blood Volume (BV)

Moves us past trailing indicators and crude and insensitive estimates

Currently we only have:

Estimates of kidney function (eGFR / based on Serum Creatinine)

Estimates of fluid responsiveness / volume

Meet requirements for FDA Expedited Review

Substantial NIH support

Investigational product not approved for human use

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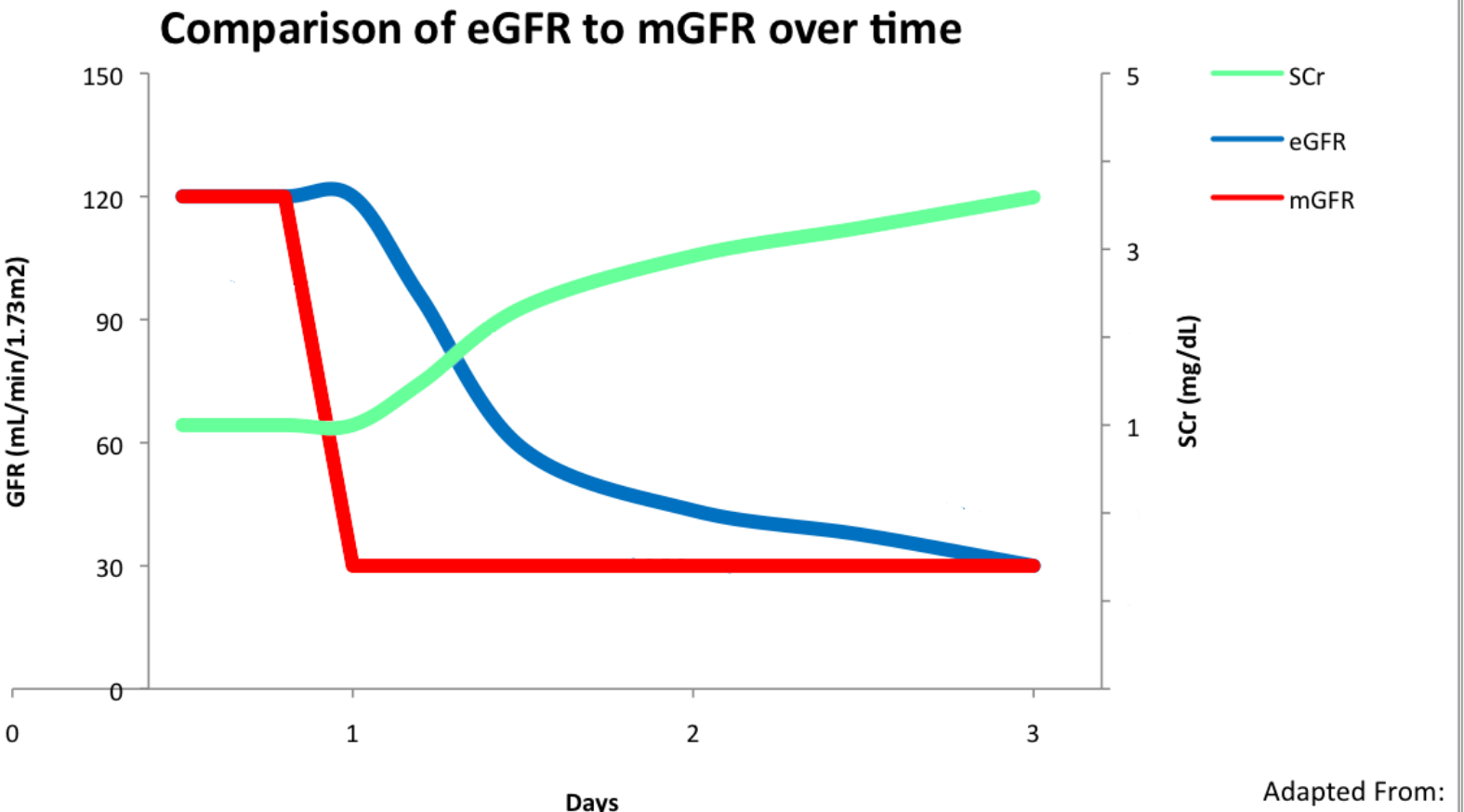
Clinical Problem – current estimates of Kidney Function

Clinical Problem

- We catch renal dysfunction too late, making it nearly impossible to time therapy to work
- We under dose and over dose renally-cleared and nephrotoxic drugs, because we can't determine renal clearance (especially in antibiotics in the ICU)
- Clinical trials for renal therapies are very difficult to conduct with the current end points of death and dialysis

>> *Direct and timely mGFR measurement could be majorly impactful*

Serum Creatinine: inaccurate trailing indicator of function days late and +/- 30% from actual



Adapted From:
Lesley A. Stevens and Andrew S. Levey
Measured GFR as a Confirmatory Test for Estimated GFR

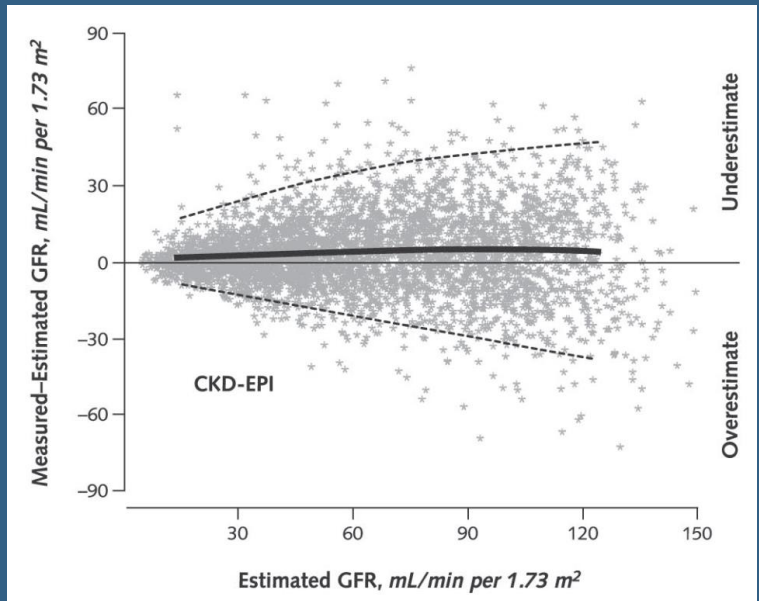
CKD- EPI

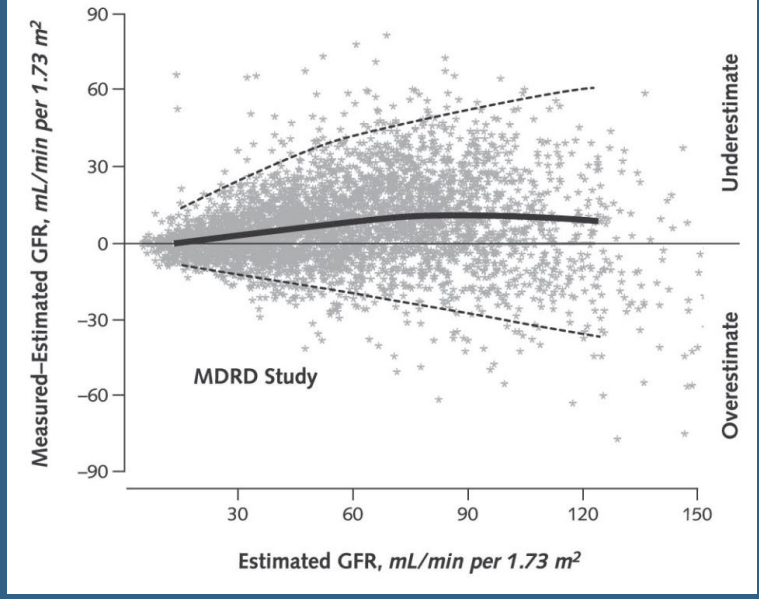
A New Equation to Estimate Glomerular Filtration Rate

Andrew S. Levey, MD; Lesley A. Stevens, MD, MS; Christopher H. Schmid, PhD;
Yaping (Lucy) Zhang, MS; Alejandro F. Castro III, MPH;
Harold I. Feldman, MD, MSCE; John W. Kusek, PhD; Paul Eggers, PhD;
Frederick Van Lente, PhD; Tom Greene, PhD; and
Josef Coresh, MD, PhD, MHS, for the CKD-EPI
(Chronic Kidney Disease Epidemiology Collaboration)*

A smoothed regression line is shown with the 95% CI (computed by using the lowest smoothing function in R), using quantile regression, excluding the lowest and highest 2.5% of estimated GFR.

Annals of Internal Medicine. 2009: 604





FAST Observations:

Extremely wide spread around the mean.

eGFR is +/- 30% of mGFR

An eGFR of 50 could be mGFR of 35 (severe disease) or 65 (stage 2 CKD)

> BIG DIFFERENCE

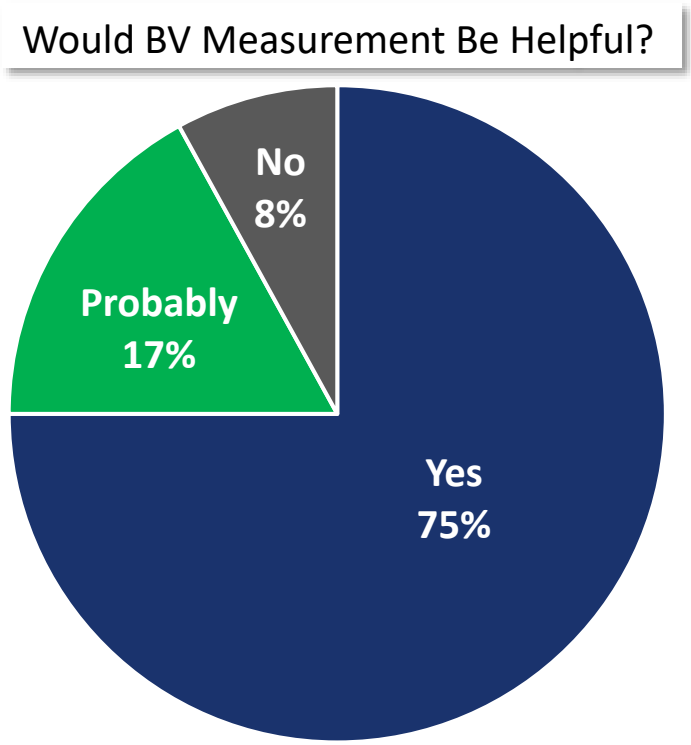
eGFR is accurate across a population,

but very inaccurate for any individual patient.

mGFR is needed for personalized / precision medicine in kidney disease

Concern Over Patient Volume Status

Clinicians see significant value in a timely and accurate BV measurement



"Absolutely. To me this is the hardest part in the ICU, especially in critically ill patients. Many of these patients have CHF or low albumin levels and I think it is just very difficult to evaluate their BV."

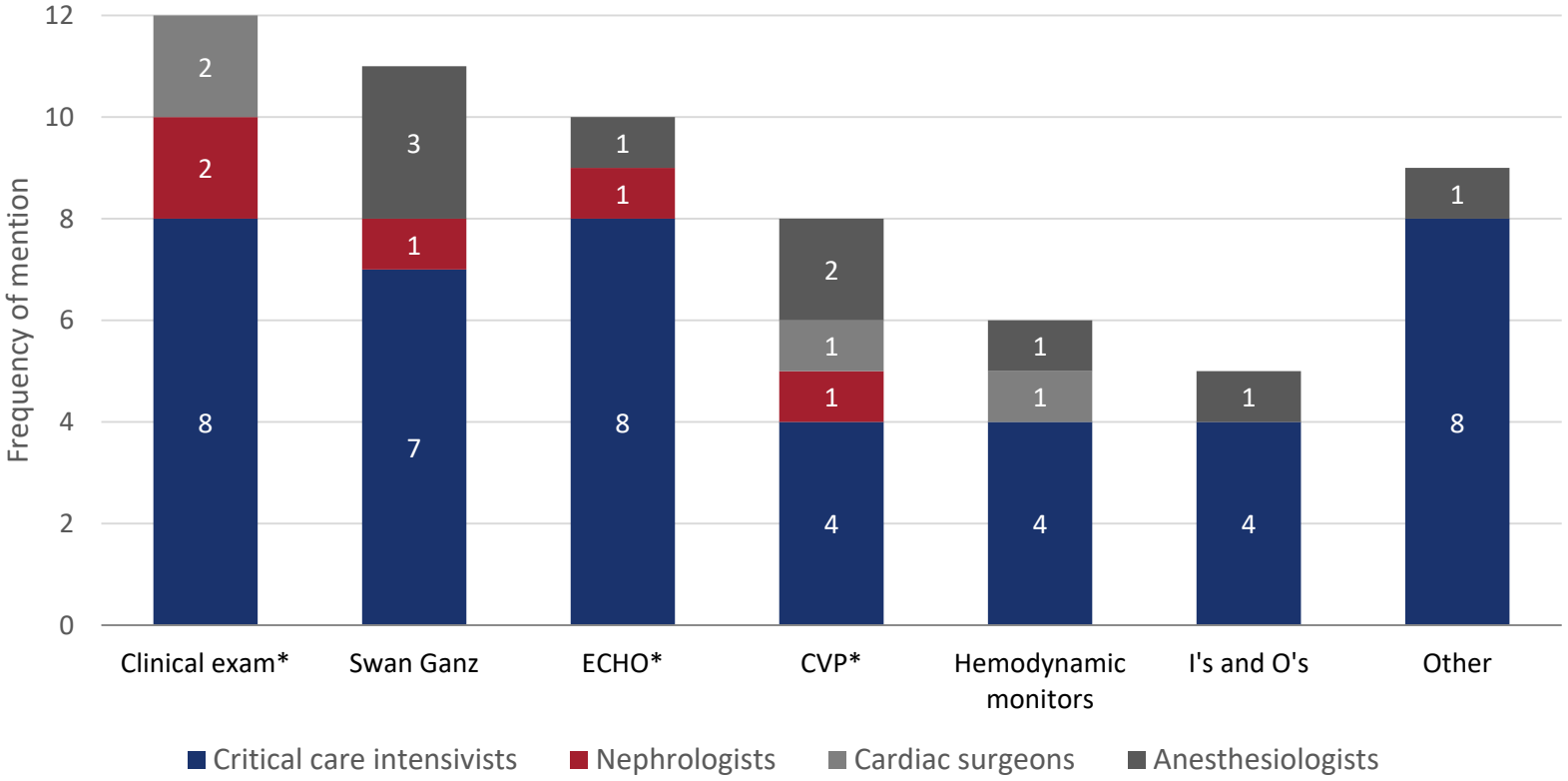
"Yes because for the post-op heart patients all of them get forced diuresis as early as post-op day one. I know one of the problems we run into is renal dysfunction because of that."

- 92% of clinicians would find BV helpful
- Clinicians want to know BV on 66-80% of patients

Source: Boston Strategic Partners primary market research

No Standard of Care for Volume Assessment

Clinical exam used more than multiple surrogate measures



Source: Boston Strategic Partners primary market research

Technology Overview

Injectable/device combination product

Visible Fluorescent Injectable (VFI)

- Single 3 mL bolus injection of 2 fluorescently-labeled carboxymethyl dextrans

Injectable: VFI Dose

BLOOD VOLUME DETERMINATION

- 150 kD dextran (12 mg) stable in vascular compartment
- One 1 mL sample at 15 minutes
- 30 minutes total turnaround time
- Plasma Volume calculated based on dilution principle
  - With hematocrit yields blood volume (PV + Hematocrit = BV)
- Provides *multiple measurements* from 1 dose for up to six hours
- Ability to dose daily for three days

KIDNEY FUNCTION DETERMINATION

- 5 kD dextran (35 mg) freely filtered by the kidney
- 2 more blood samples over 170 minutes

Medical Device Development – Generations 1 & 2

Fluorescence-based device – MOSTLY COMPLETE

- **<u>For use in Pivotal study and first commercial product</u>**
- Lab-based, compatible with workflow
- Time from sample to result:

  30-45 minutes (BV), 3hrs 15 min (mGFR)
- Critical optics components completed

Fluorescence-Based Device

Fully automated fluorescence-based device

- Based on initial fluorescence device
- Suited for lab or near bedside

Automated Fluorescence-Based Device


Distribution and Clearance
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Distribution and Clearance

How mGFR and BV might impact patients

- **Transplant Patients**
  - Better evaluation of living donors to increase the # of organs for candidates
  - Better evaluation of renal patients
    - eGFR over estimates function = delay in transplant referral
  - Enable post transplant monitoring of function
  - Improves specificity of dosing of immunosuppressants
    - Better dosing of all renally cleared and/or renally toxic drugs

All Renal Patients

  - Enables measuring renal reserve to identify risk of progression
  - A better endpoint for clinical trials (vs. death and dialysis)
  - A better way to detect early onset, and stage patients for treatment and trials
- **ESRD Patients**
  - BV can help establish dry weight = manage volume better
    - Weight is a guide taking off of fluid
  - Delay ESRD by better management of CKD

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Clinical History

- 97 patients over 3 clinical studies
- Phase 2 complete
- Locations : Ulm, Germany; Birmingham, Alabama; and San Antonio, Texas

- Patient populations: Healthy Volunteers, Subjects with CKD 3 and 4.
  - Comorbidities included: hypertension, diabetes, COPD, coronary artery disease

- VFI was well tolerated in all populations. No SAE's reported
- Extremely accurate, repeatable, and sensitive
- Primary and secondary endpoints achieved

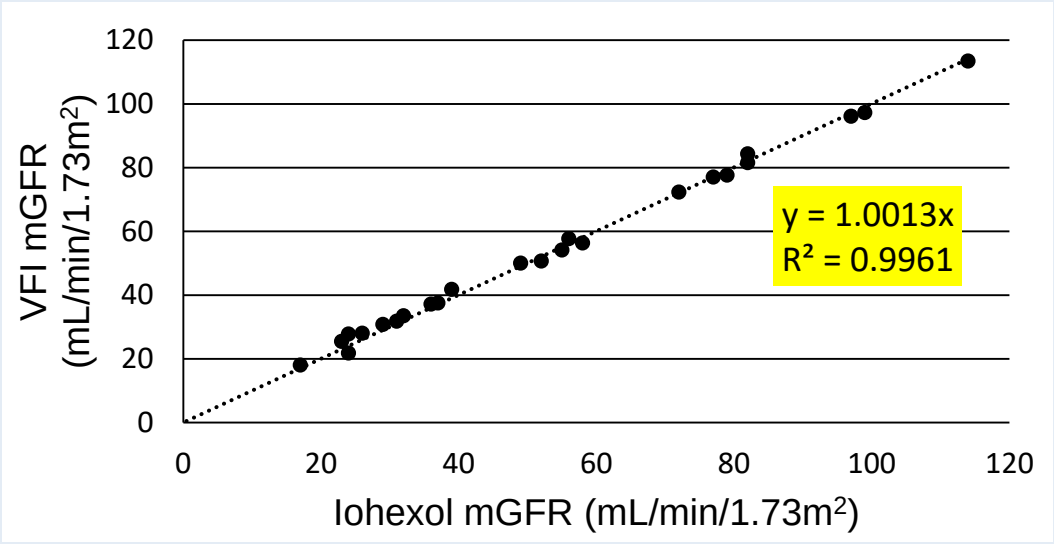
Novel technology allows accurate and rapid measurement of mGFR

METHODS: 32 subjects were enrolled in this Phase 2b study. mGFRs were determined using the FAST BioMedical VFI™ technology and Iohexol clearance. The large marker in the VFI is retained in the vasculature and used to measure plasma volume, a key metric in measuring GFR quickly and accurately.

Cohort 1	Cohort 2	Cohort 3	Cohort 4
			
8 Healthy Subjects	8 Healthy Subjects	8 CKD Stage 3 Subjects	8 CKD Stage 4 Subjects

VFI : 3ml injection of large & small fluorescent markers Three blood samples: 15, 60, 170 minutes.
Iohexol : 5mL injection (Omnipaque 300). Blood samples: 120, 150, 180, 210, 320 minutes.

RESULTS: VFI mGFR showed near perfect linear correlation when compared to Iohexol mGFR across wide range of kidney function.



CONCLUSION: VFI™ is a safe technology that allows the accurate, rapid and highly reproducible measurement of GFR and PV at the bedside in healthy volunteers and across a wide range of kidney function.

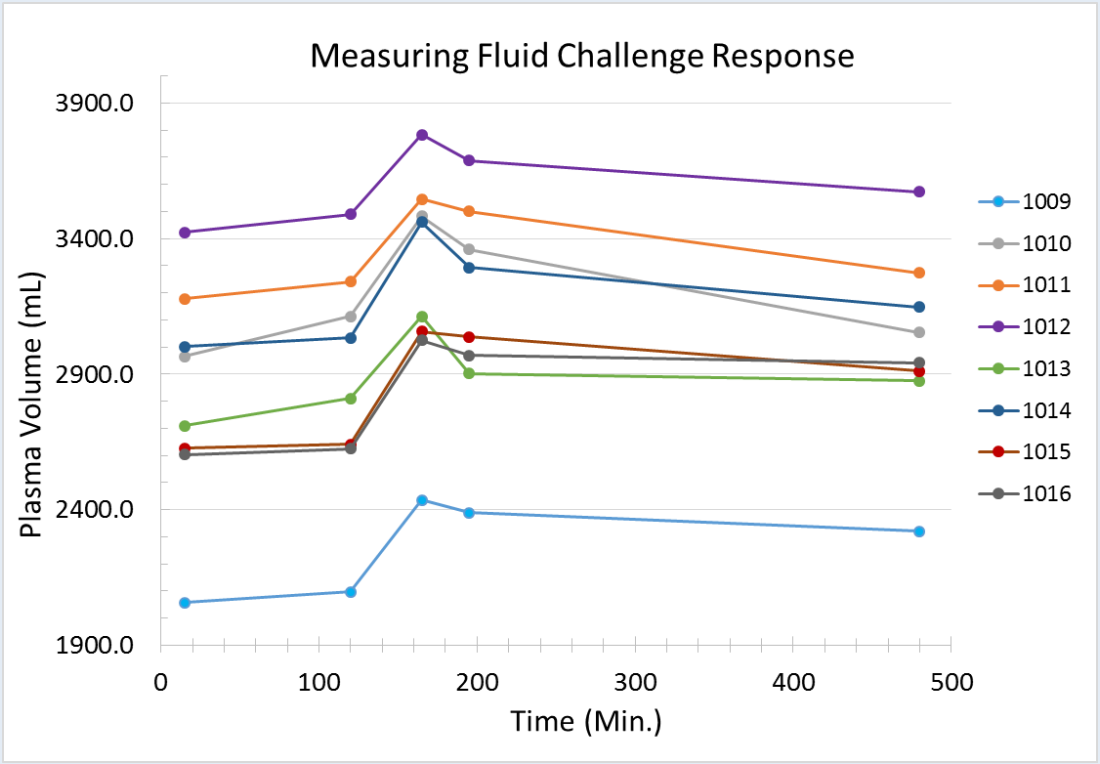
doi: 10.1681/ASN.

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Plasma Volume Measurement – Pilot / Phase 2b – Volume Challenge

METHODS: 32 subjects were enrolled in this Phase 2b study. 8 healthy volunteers received a 350mL, 5% albumin challenge administered 130 minutes after VFI dose/. A 3mL injection of VFI was given at 0 minutes. No additional VFI was dosed prior to the volume challenge.

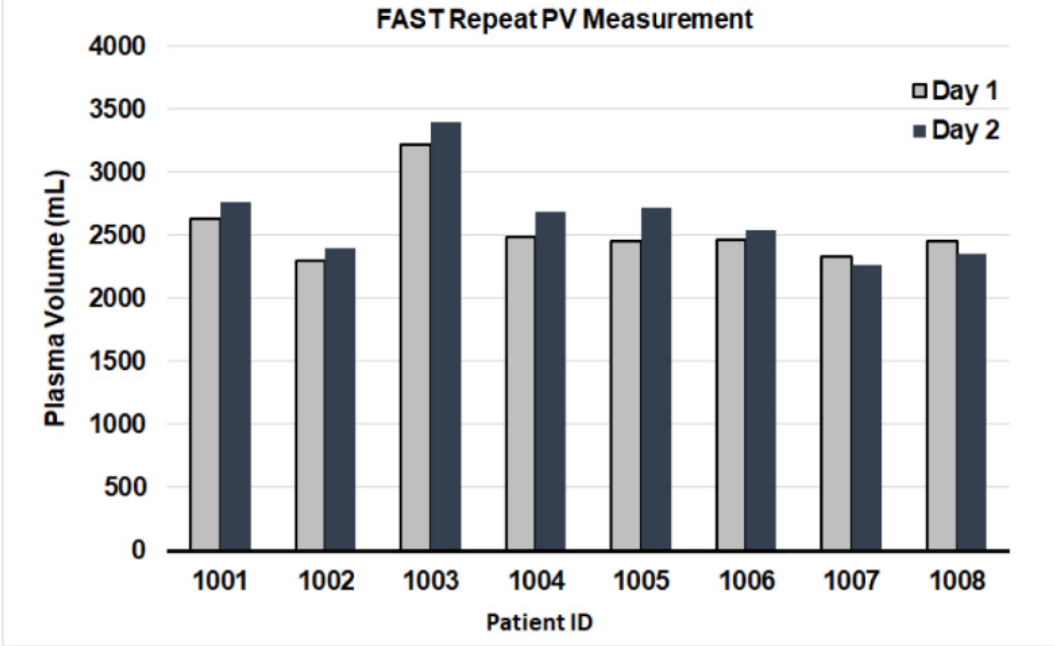
RESULTS: VFI PV showed near perfect correlation when compared to the volume challenge given. An average increase of 354mL was measured



CONCLUSION: VFI™ is a safe technology that allows the accurate, rapid and highly reproducible measurement of PV, even during a dynamic change in volume.

Plasma Volume Measurement – Pilot / Phase 2b – Repeat Measure

METHODS: 32 subjects were enrolled in this Phase 2b study. 8 healthy volunteers received a 3mL injection of VFI from which the PV was measured. 24 hours later each subject received a second 3mL VFI dose and a second PV was measured. Subjects were resident in the CRU with a controlled diet to limit known impactors on volume status.



RESULTS: VFI PV showed excellent repeatability between days and with additional dosing. As expected there were no significant changes to PV.

CONCLUSION: VFI™ is a safe technology that allows the accurate, rapid and highly reproducible measurement of PV.

Regulatory Approval & Clinical Trial Plan

NEXT STEPS

Currently in a Pilot / Phase 2c Trial

- Lead into pivotal trial
  - Heart failure
  - CardioRenal
  - 50 patients
  - Generate observational data

Pivotal Trial for regulatory clearance

- Multi-site study
- Continue to demonstrate safety and achieve endpoints

<u>33 month timeline from next round of financing</u>

- Scale up injectable and refine device into final commercial form
- Prepare for and conduct a Pivotal trial
- File PMA to achieve regulatory clearance

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Deep Domain Expertise

Strong KOLs in critical care, heart failure, cardio-renal

Medical Advisory Board

- Dr. Andrew Shaw – University of Alberta
- Dr. Frank Peacock – Baylor
- Dr. Patrick Murray – UCD Dublin School of Medicine
- Dr. Erin Barreto – Mayo Clinic
- Dr. Bruce Molitoris -- Indiana University School of Medicine / VA

Barriers in Kidney Health

JASN

- J Am Soc Nephrol. 2016 Jul; 27(7): 1902–1910.
- Published online 2016 Apr 28. doi: 10.1681/ASN.2015090976
- PMCID: PMC4926987
- PMID: 27127187
- **Overcoming Barriers in Kidney Health—Forging a Platform for Innovation**
- Linde PG, Archdeacon P, Breyer MD, Ibrahim T, Inrig JK, Kewalramani R, Lee CC, Neuland CY, Roy-Chaudhury P, Sloand JA, Meyer R, Smith KA, Snook J, West M, Falk RJ. Overcoming barriers in kidney health-forging a platform for innovation. J Am Soc Nephrol : 1902–1910, 2016

- ***Kidney disease is a global health care epidemic***. However, the kidney community has generated fewer randomized, controlled trials than ***any*** internal medicine specialty, produced a limited number of innovative drugs and devices, and ***received less funding from public and private sources compared with other diseases***.

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Silicon Valley Bank

Trends in Healthcare Investments and Exits 2018

Innovation Wave Drives Robust Activity

MID-YEAR REPORT 2018

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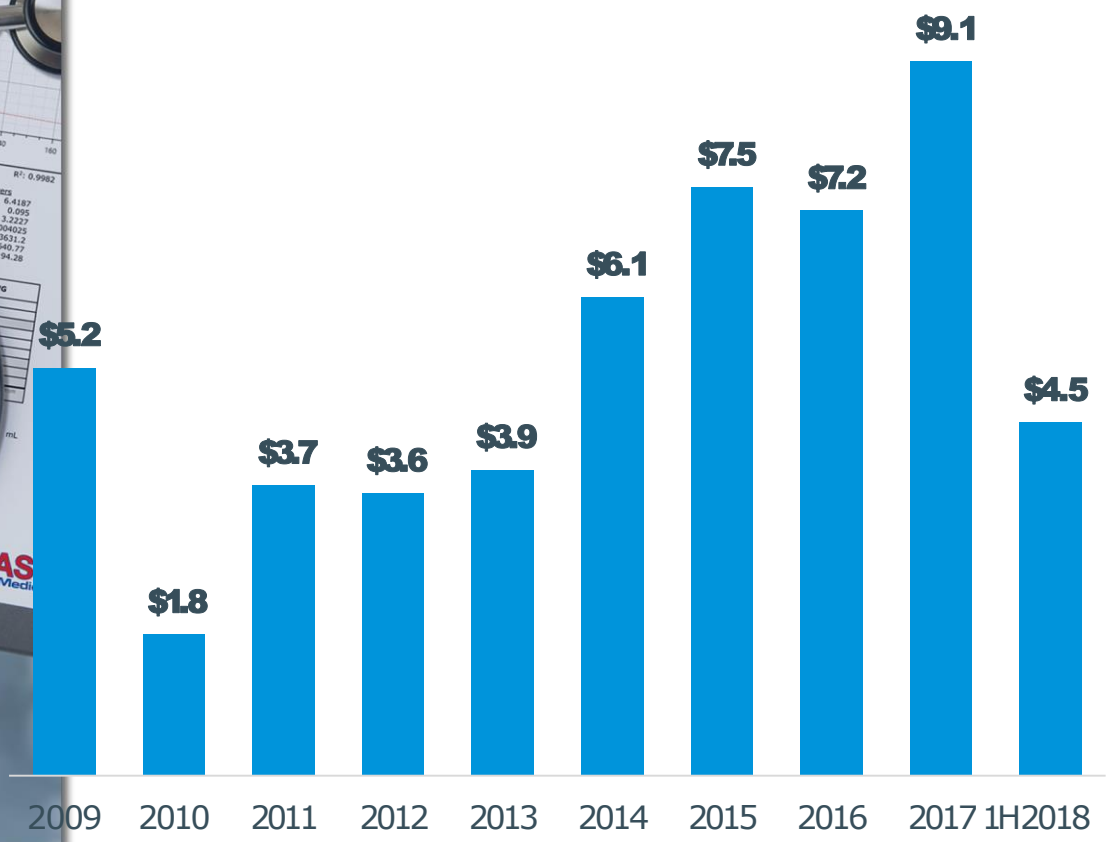
U.S. HCVenture Fundraising Stays on Torrid Pace

U.S. Healthcare Venture Fundraising*, 2009 – 2018

HCVC$ Fundraised
($ BILLIONS)



Fundraising is on pace to match the 2017 total of $9.1B – counter to our early 2018 prediction that the annual total would decline. A confluence of events is driving investment and fundraising to new levels. Rapid technological advances, leading to clinical breakthroughs, are benefiting patients and investors alike. In this environment, quick exits are underpinning an explosion of activity, particularly in biopharma, attracting new pools of capital and giant investments by traditional and non-traditional investors, including tech investors.

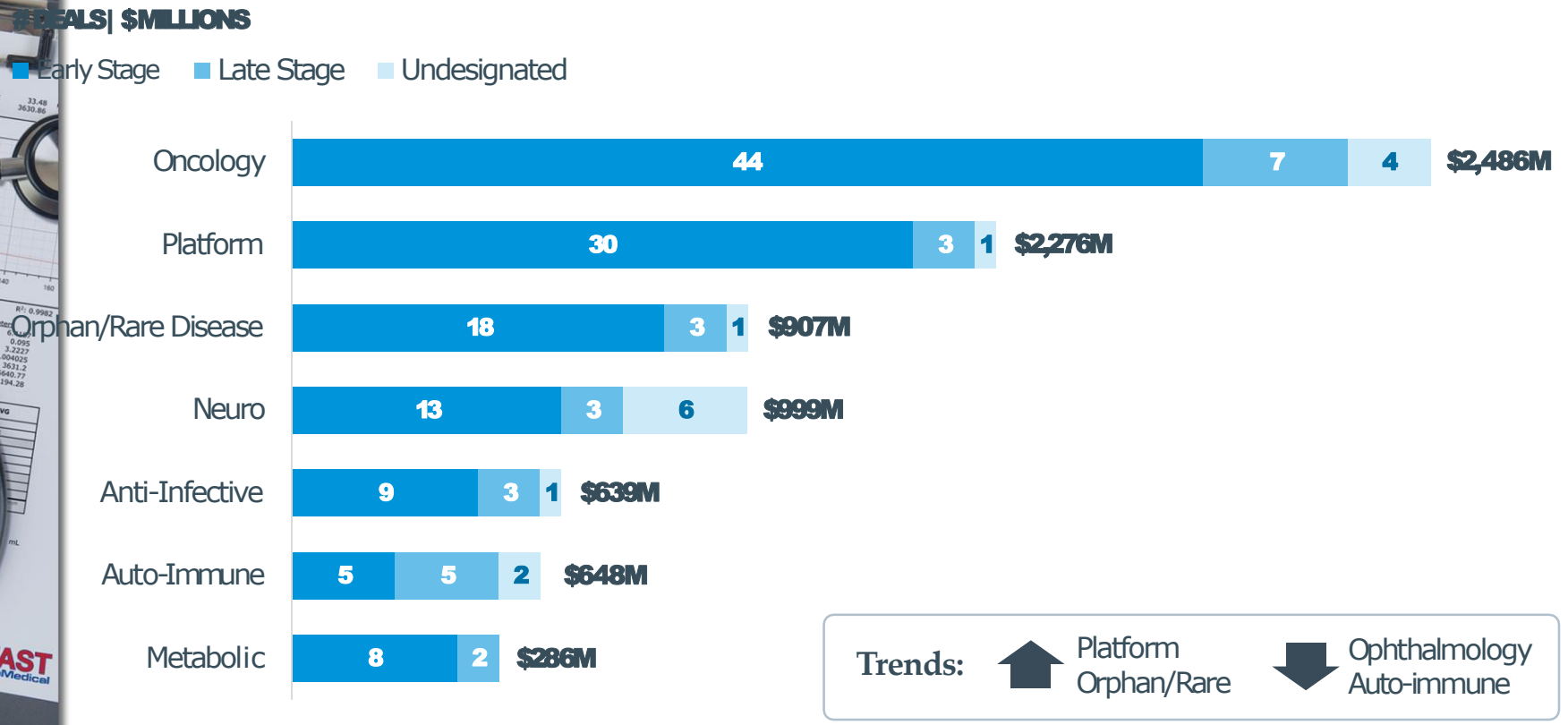
With the entry of artificial intelligence (AI) and machine learning (ML), these tech investors see huge opportunities in drug development and the tools required to help identify cures for a range of diseases.

The biopharma IPO window is rewarding investors with quick valuation step-ups (many companies had IPOs within two to three years of Series A). This path to liquidity is translating into renewed excitement by limited partners who are eager to keep the investment cycle going by supporting larger venture fundraises at a faster pace.

*SVB calculates only the dollars allocated to healthcare by U.S. venture funds or funds investing primarily in the U.S.
Source: PitchBook and SVB proprietary data.

Oncology and Platform Deals Capture Most Interest

Most Active New Investments* in Biopharma by Indication, 2017 – 1H 2018



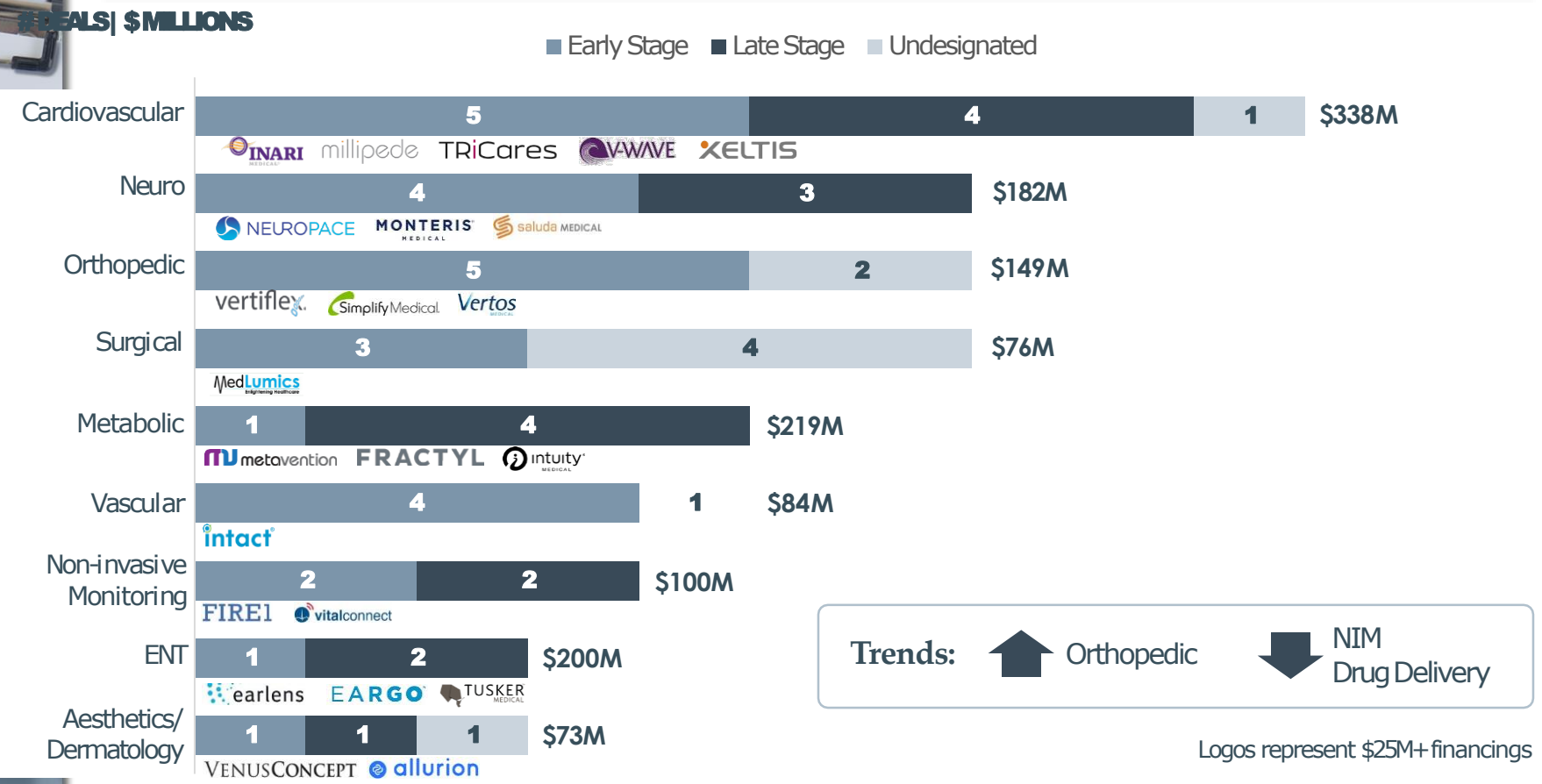
Underscoring the recent influx of capital over the past two years from the most active investors, every top indication in 1H 2018 other than oncology has already surpassed investment levels for full-year 2016.

Waves of new biopharma investment are pushing funding for platform companies to levels similar to oncology and driving a comeback for orphan/rare drugs.

*Most Active New Investments in biopharma defined as Top 60 venture and corporate investors based on new investments in 2016–2017. Platform companies have technologies with multiple or non specified indications. Early Stage defined as Series A & B; Late Stage defined as Series C and later. Financing data through 6/15/18.
Source: PitchBook and SVB proprietary data.

Device Investing Stays Consistent

Most Active Device Investors by Indication*, 2017 – 1H 2018



Aesthetics/
Dermatology

While active investor activity by indication is closely mirroring previous years, non-invasive monitoring (which has received a lot of early stage Series A interest) and drug delivery investment have not scaled as expected.

Three neuro IPOs and a pair of uro/gyn M&A deals may spur additional interest in those areas.

*Most Active Device Investors defined as Top 35 venture and corporate investors calculated as new investments into companies in 2016 – 2017.
Early Stage defined as Series A & B; Late Stage defined as Series C and later.
Financing data through 6/15/18.
Source: PitchBook and SVB proprietary data.

Summary

- Moving from estimates to measurements of kidney function is an important step in bringing precision medicine to kidney disease
- These mGFR and BV technologies could favorably impact transplant patients and the broader renal care community
- Accurate and timely measurements of kidney function and blood volume are in late clinical stage development
- The renal arena / kidney disease is grossly underfunded compared to other less prevalent and damaging disease states = stifling innovation

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