MHIF FEATURED STUDY:  
Heart EXPAND CAP

DESCRIPTION: A single-arm study evaluating the OCS™ Heart System and extended criteria donor hearts (those that are currently not transplanted or are seldom transplanted in the US)

CRITERIA LIST/QUALIFICATIONS:

Donor Heart Inclusion
- Expected total cross-clamp time of ≥4 hours; OR expected total cross-clamp time of ≥2 hours PLUS one of the following risk factors:
  - Donor age 45-55 years, inclusive, with no coronary catheterization data
  - Donor age ≥55 years
  - Left ventricular septal or posterior wall thickness of >12 mm, but ≤16 mm
  - Reported down time of ≥20 min, with stable hemodynamics at time of final assessment
  - Left heart ejection fraction (EF) ≥40%, but ≤50% at time of acceptance of offer
  - Donor angiogram with luminal irregularities with no significant CAD (≤50%)
  - History of carbon monoxide poisoning with good cardiac function at time of donor assessment
  - Social history of alcoholism with good cardiac function at time of donor assessment
  - History of diabetes without significant CAD on angiogram (≤50%)

To date, MHIF has had four successful uses of the TransMedics Organ Care System (OCS™), aka “Heart in the Box”
MHIF FEATURED STUDY:
Heart DCD

DESCRIPTION:
To evaluate the effectiveness of the OCS Heart System to resuscitate, preserve and assess hearts donated after circulatory death for transplantation to increase the pool of donor hearts available for transplantation.

A prospective, randomized and concurrent controlled, non-inferiority pivotal trial in which subjects who receive a DCD donor heart transplant will be compared to subjects who receive a standard criteria donor heart transplant (SOC1 and SOC2 - from both randomized and concurrent control groups), adjusting for differences in risk factors.

CRITERIA LIST/QUALIFICATIONS:
Donor Heart Inclusion
- Maastricht Category III DCD donor, defined as expected death after the withdrawal of lifesupportive therapy (WLST)
- Donor age 18-49 years old inclusive
- Warm ischemic time (WIT) ≤ 30 mins, with warm ischemic time defined as: Time from when mean systolic blood pressure (SBP) is < 50 mmHg or peripheral saturation < 70% to aortic crossclamp
- and administration of cold cardioplegia in the donor.

To date, MHIF has had four successful uses of the TransMedics Organ Care System (OCS™), aka “Heart in the Box”

CONDITION: Heart Failure/Transplant
PI: Karl Mudy, MD

RESEARCH CONTACTS:
Kari Thomas - Kari.M.Thomas@allina.com | 612-863-7493
Kari Williams - Kari.Williams@allina.com | 612-863-0027

SPONSOR: TransMedics, Inc.
What does the heart have to do? (My list)

- Be built
- Grow
- Low energy at rest
- High output at stress
- Adapt
- Evolutionary toolkit
Cardiology is being left behind by other domains eg Cancer

Measurement is imprecise
Not measuring biology and pathways
Not reaching all patients
Poor Standardization
Poor linking to therapy
Poor integration with other data

Myocardium – the single greatest opportunity in medicine

The heart of cardiology
- an emergent problem
Precision therapy?
- Not one approved myocardium targeted therapy
- millions get the same 4 drugs
- our studies fail
Control not cure
- cardiology becoming un-investable
Other domains transformed
- cancer: industrialized, linked, redefined, biofluids, personalized therapies
Cardiology silos
- no shared language: open source frameworks, “opinion based” domains
- genetics not actionned
- disease definitions imaging based
- 2 biofluid markers
We gamble
- massive endpoint phase III trials
- drug approvals falling
Exploration at many scales

Structure and function
Tissue characterisation
Genetics
Blood biomarkers
ECG

The Myocyte

~13 contractile proteins
5000 proteins
Of ~26000 genes
Mutate each one: 15% - cardiac phenotype
A pair of cells: the Myocyte and Capillary

Fundamental building block


Right Ventricle Vasculature in Human Pulmonary Hypertension Assessed by Stereology.

Graham BB1, Tuder RM1

---

Myocytes into Fibrils

Myoarchitectural disarray of hypertrophic cardiomyopathy begins pre-birth

Canadilla...Moon.. Captur G. J Anatomy 2019
“Nature uses only the longest threads to weave her patterns, so each small piece of her fabric reveals the organization of the entire tapestry.” Richard Feynman
Cardio-morphogenesis: Building a heart

Episcopic microscopy. E14.5 to 16.5 mouse embryo (1mm long). Acknowledgements: Gaby Captur

Post septation
Compaction

Imaging underpins cardiac care
Imaging modalities
Structure and function - Defined by morphology/function

The basics: not well done

- Echo
- MUGA
- CMR

Bellenger 2000
Accuracy vs Precision

Where am I now?

Vs

How have things changed?

Oncology patients undergoing screening for cardiotoxicity

Referred for MUGA

Referred for CMR/echo

Group 1

Group 2

Group 3

Precision
Test-rest reproducibility of ejection fraction
N=78; 312 assessments

Charlotte Manisty
Precision: MUGA vs Echo vs CMR

2D echo inadequate for detecting EF changes
But the others not that good

Menacho, Bhuva, Moon, Manisty submitted

Other parameters eg LVH?

2

10 perfect echo and CMR datasets
20 centres
69 experts

Conclusion:
Current wall thickness measurement:
Unacceptable as a clinical test

Or:
Global experts: talk not do (technicians)
Far more complex process occurring
(integrated opinion, then justify with 2D measurement)

Submitted
Gaby Captur + 15 others
AI Revolution

a world run by geeks

Medicine is lagging behind

Images: Convolutional Neural Networks

Multilayered computation circuits copy the architecture of the visual cortex

CIFAR-10: 60,000 images
10 classes 32x32x3

No hard coding
learns features for itself

ImageNet Error Rate

Image classification

Best performance: <2% error rate
A revolution driven by multiple developments

- Neuroscience
- Compute power esp GPUs
- Data availability
- Data sharing
- New Computer languages
  - Universities
  - Industry
- Competitions
- Open publication arXive

AI Revolution: not just classification segmentation

Object detection, labelling, pose, relationships, complex reasoning
Favourite resource:
1. Youtube: 3blue1brown series 3

Then
2. Youtube: CS231n lecture series Stanford

Progress is incredibly rapid

Youtube: Stanford course CS231n
GPU+vector based high level languages
1000 patient volume studies, EF

The total prize pool for this competition is $200,000, distributed as follows:
- 1st place - $125,000
- 2nd place - $50,000
- 3rd place - $25,000

RMS Error

<table>
<thead>
<tr>
<th>Tencia_Woshialex</th>
<th>Diastolic</th>
<th>12.02 mL</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>10.19 mL</td>
</tr>
<tr>
<td></td>
<td>E Fraction (%)</td>
<td>4.88 %</td>
</tr>
</tbody>
</table>

Richard Waisman in San Francisco MAR 30, 2016

Hedge funds ‘quants’ win heart diagnosis challenge
Tencia Lee and Qi Liu formulate algorithm to spot cardiac disease on MRI images

Paper 1

Automated cardiovascular magnetic resonance image analysis with fully convolutional networks

N=5000
Health
Single magnet
Comparison with human contours

To product – for speed
Paper 2,3,4 – generalise, measure and improve performance

Performance equalling human – any disease

Bhuva A.. Manisty C. In press Circ Imaging 2019

Can AI be Superhuman?
Superhuman Cardiac segmentation for LV structure and function

What we did

Aiming for Superhuman (Output > human)

Why?
Bug?
Inadequate model?
Inaccurate training data?

Identify cause
Resegment

“Turing Test”
Would a human do that

Sample (fold) eg n=400
Review tools

Superhuman test

Hold-out data, independent teams

Precision dataset: Test re-test
N=130, 5 centres, any disease
Anonymised
Annotated by trainee and expert
Scan A, scan B, scan C
23,000 contours

Outcome dataset
N=1500
Single centre, USA
Anonymised
Alive/dead/MACE known
(n=295 outcomes)

Error classification

Prediction (CoV, trial size) vs human

Predictive power vs human

Precision: 50% better than human
Prediction: Better than human
New biology: EF beaten by MCF

Training data
Consented medical imaging
Representative

Class
Normal
Dilated
Hypertrophied
Impaired

Manufacturer
Siemens
Philips
GE

Field
1.5T
3.0T

Representative Disease Manufacturer Field
Normal Siemens 1.5T
Dilated Philips 3.0T
Hypertrophied GE
Impaired Global/Regional

Trustworthy Research Environment
1923 patients
14 institutions
3,000,000 images
900,000 cine images

Superhuman test

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N=1500
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ML algorithm

Short axis

Long axis

Training data
Consented medical imaging
Representative

Class
Normal
Dilated
Hypertrophied
Impaired

Manufacturer
Siemens
Philips
GE

Field
1.5T
3.0T

Representative Disease Manufacturer Field
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ML algorithm

Short axis

Long axis

Valve plane

Keep

Discard

 Apex

Base
Latest work: Almost never wrong

1. Sax view
2. Breast implants
3. Mis-segmentation
How do you Evaluate Model Performance?

• Measure agreement of model vs human  
  • e.g. DICE metric, Haussdorf distance

But... are humans always right?

Hold-out validation datasets
  • 1. Precision
  • 2. Prediction clinical outcomes
Precision

• 110 patients
• Multi-institution
• Multiple pathologies
• Scanned
  • then scanned again
• Expert vs machine

Scan
EF 56%

Rescan
EF 58%

Example of ML algorithm segmentation

https://thevolumesresource.com

Precision: Intra-observer Reliability

Exact same images twice
ML algorithm has no variation
same image  ⇒  same answer

https://thevolumesresource.com
Precision: Scan Re-scan Repeatability

Translates to clinical trials:
• to detect 3% change in EF
  ⇒ need 40% fewer subjects

Predicting Clinical Outcome

• 1,277 patients
• Clinical service
• CMR
• Clinical outcomes
  • Death
  • Hospital admission with heart failure
• 5.5 year median follow-up
  • 29% event rate
Predicting Clinical Outcome

- Cox regression analysis
  - LV metrics vs outcome
  - $\chi^2 \propto$ strength of association

<table>
<thead>
<tr>
<th>Multivariate</th>
<th>Univariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human expert</td>
<td>ML algorithm</td>
</tr>
</tbody>
</table>

Myocardial contraction fraction ($MCF$) = \[\frac{\text{stroke volume}}{\text{myocardial volume}}\]

Al: a mirror to see ourselves

AI approach:
- more precision, all parameters
- Prognosis better prediction for overall model
- MCF beats EF
- one outlier: human EF beats machine

Humans primary task is are not measuring EF
- a service
- integration of datasources
- trying to influence decision making
2013
Breast Ca + mets
Her2 +ve
Surgery + Chemo
then
Herceptin for life + cardiac monitoring
~55,000 patients pa
Infarction, heart failure, cardiomyopathy
1 million echos
100,000 CMR

Future Phase 1
Machine analysis
+40% precision

Future: Phase 2
+ Autonomous scanning
+ New imaging biomarkers

Example

Current

Future: Phase 2

Scan
2013
2014
2015
Scan
2016
2017
Scan
2018
2019
Stop Chemo

Echo
CMR
64%
68%
65%
67%
62%
60%
56%
57%
57%
56%
54%
54%
51%
46%
51%
44%
43%
44%
46%
56%
60%
64%
72%

A new definition
Streamline
Equipotential Surface
Wall thickness – preliminary results

Measuring heart maximum wall thickness
12 credible international experts
- 4 continents
in 60 HCM patients
  - scanned twice
  - 5 different scanners
  - multiple institutions

AI beats not just one human, but all humans

Cardiac Wall Thickness

Figure 4. Test: retest Bland-Altman limits of agreement (LOA, mean bias ± 1.96 SD) for each expert (1 – 11, blue) and machine learning (ML, green). The average LOA for all experts is shown in red. The difference between the upper and lower LOAs is displayed in each bar. The LOA for ML was less than half of the average expert LOA.
Initial success:

Fast feedback tools for AI
Expert imagers needed – capturing what you do
Democratising process

Here fast training “which view is 4ch”

Francis DP group, Imperial
AI in imaging will cascade benefit through cardiology

Solutions generalise
Faster
More accurate, more precise
Humans stop mundane per patient analysis processes

Instead 2 things:
a) Quality control and oversight
b) Training: not just junior doctors, but networks

Things no-one tells you: engineering:clinical
1. Medicine is about unique outliers not big data: I want outliers not big data
2. Missing data is missing for a reason
3. Your language is not my language (precision?)
4. Doctors are not doing what they say they are doing

AI penetration of healthcare currently low
But this is changing:
Imaging: All our research now has AI in it

Peter Kellman Hui Xue, Rhodri Davies. NIH: Barts
Myocardial biology – processes

- normal
- infarction
- diffuse fibrosis
- myocarditis
- disarray
- Fabrys
- amyloid
- iron

Dozens more types. Different stains, different cameras

Speakers own cases

Framework for Pathological processes

Primary Processes
- Direct Myocardial Storage
  - myocytes (subtypes)
  - endothelial cells
  - fibroblasts, smooth muscle, immune cells
- Remote disease
  - autonomic
  - vascular
  - renal
- Other effects
  - non-storage toxic effect
    (systemic/paracrine)

Primary Processes
- Direct Myocardial Storage
  - myocytes (subtypes)
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- Remote disease
  - autonomic
  - vascular
  - renal
- Other effects
  - non-storage toxic effect
    (systemic/paracrine)

Secondary Processes
- Key pathways
  - “Buffering”
  - hypertrophy
  - cell death
  - inflammation
  - fibrosis
  - 100x other pathways
- Impact classification
  - adaptive/maladaptive
  - reversible/irreversible
  - druggable/non druggable

Primary Consequences
- Mechanical
  - Gain/loss of function
  - Adaptability
  - Efficiency

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- Mechanical
  - Gain/loss of function
  - Adaptability
  - Efficiency

Secondary Consequences
- Symptoms
  - Fatigue
  - Exercise limitation
  - Chest pain

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- Symptoms
  - Fatigue
  - Exercise limitation
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Modifiers
- Age
- Sex
- Multimorbidity
- Therapy

Risk
- Heart failure
- Sudden death

Here Fabrys
Single parameter: native T1 mapping quiz
What's the disease?

Normal  HCM  Fabry  Hypertension  Myocarditis

Adapted from M Under concept slide 2014
1.5 T Longitudinal multi-site, multi-vendor T1 mapping T1MES data*
Temp-adjusted (21°C) CoV/tube for 1.5 T T1 mapping sequences according to vendor/scheme/WIP#

Vendor | sequence ranking order by CoV (1.5 T)
----- | ---------------------------------
SIEMENS | MOLLI 5s(3s)3s [448B] 0.27 BEST CoV
PHILIPS | MOLLI 3s(3s)5s 0.54
SIEMENS | SASHA 0.56
SIEMENS | SHMOLLI [1041B] 0.64
PHILIPS | SASHA 0.92
PHILIPS | ShMOLLI 1.04
GE | MOLLI 5b(3s)5b 1.28
GE | SMART 3.00

*Kapur G, Moon JC 50 others et al. in review #4

Kellman analysis data (from Kozor, Moon)
Kellman analysis data (from Kozor, Moon)

Not just CMR, not just mapping

Amyloid in 1 in 7 TAVR patients

JACC 2018
Castano EHJ 2017

Multimodality approaches, published yesterday
https://doi.org/10.1007/s12350-019-01760-6
AS and AS-amyloid – a program

Single centre
Multicentre
Registry
Outcome
Therapy

Tom Treibel
Joal Cavalcante

Coronary Circulation and Microcirculation

Maria Siebes, PhD
Dept. of Biomedical Engineering & Physics
CMR Quantitative Perfusion Mapping

- AIF curve
- BTEX model: \[ \frac{dC}{dt} = \frac{1}{V_s} \left[ \frac{1}{CFL} \frac{dC}{dt} + \left( C - C_{residual} \right) \right] \]
- Compare with measured Gd residual signal and update model parameters

Flow map (ml/min/g)
PS map (ml/min/g)
Extraction fraction map
Blood volume map (ml/g)
Interstitial volume map (ml/g)

Slide courtesy of Peter Kellman
Hypertrophic cardiomyopathy - Apical

AI feature extraction

AI segmentation

technical reporting

Gadolinium Report

<p>| | |</p>
<table>
<thead>
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<tr>
<td>Stress HR</td>
<td>71</td>
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<tr>
<td>Pre-stress HR</td>
<td>81</td>
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<tr>
<td>HR increase</td>
<td>-32.0%</td>
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<tr>
<td>AF peak (ms)</td>
<td>1.8</td>
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<tr>
<td>AF first pass EKG/SM</td>
<td>11.8 sec</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Heavy</td>
</tr>
<tr>
<td>WARNING</td>
<td>None AF detected</td>
</tr>
</tbody>
</table>
Reaching more patients

More information per study
Faster
Cheaper
Easier
More available
More situations

1% of all MRI scans should be for cardiac device patients

Our Mission

Our mission is to ensure that patients with cardiac devices have the same access to MRI scanning as everyone else.

"You have the right to receive care and treatment that is appropriate to you." — The Nuffield Constitution

You can find out what we do here and why we are doing this here.

Our campaign is grateful for the support of doctors, patients, and hospitals and medical societies. Get involved by either telling us about your hospital, using our resources, or anything else.
MRI for any patient with any pacemaker or ICD
- Wide Band LGE for ICD patients

CMR in 10 minutes
  Reaching new patients

Amna Abdel-Gadir and Hatai Ngamkasem (London/Thailand)
New biomarkers – integrating with imaging

**HCM Myocardium Proteomics**
Discovery proteomics in 11 HCM and 6 controls

**HCM Plasma Proteomics**
Plasma profiling proteomics in 16 HCM and 12 controls

**Literature Search**
Peptides of interest in the reported literature

- Multiplex LC-MS/MS Serum Peptide assay
- Training Dataset
  - 80 HCM and 67 controls
- Validation Dataset
  - 30 HCM and 30 controls
- 6 Markers validate ($P < 0.006$) for identifying HCM

Predicts HCM (vs controls)
AUC 0.87
Correlates with:
- wall thickness
- 4 biomarkers correlate with NSVT
- 5 year predicted risk

Identification of a Multiplex Biomarker Panel for Hypertrophic Cardiomyopathy using Quantitative Proteomics and Machine Learning

6 biomarkers
10 µl plasma
10 minute LC-MS/MS

Submitted
Conclusion

We have problems in Cardiology
- falling behind other fields for therapies
- our imaging not good as we think
- need to measure pathways and biology better
A framework for proceeding

AI is transforming imaging
- a revolution - stay on board
- all modalities
- changing imaging, changing cardiology

Other area:
- reaching more patients
- faster cheaper easier
- standardization

New frontiers:
- Integrating imaging with other datasources
- linking centres together

Transforming care

james@moonmail.co.uk