Developing Personalized Medicine Strategies in Scleroderma

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Disclosures

Clinical Trial Steering Committee (Eicos)

Research grant funding from Kadmon Corporation LLC, Eicos Sciences, Arena Pharmaceuticals and Medpace for clinical trials

I will not reference unlabeled or unapproved uses of drugs or other products.

The following patents/applications are related to this presentation:

- -Autoimmune Antigens and Cancer
- -Materials and Methods for Assessing Cancer Risk and Treating Cancer
- -Interactive Tool to Improve Risk Prediction and Clinical Care for a Disease That Affects Multiple Organs.

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Scleroderma is a shrinking skin of steel

In its more aggravated forms diffuse scleroderma is one of the most terrible of all human ills. Like Tithonus to "wither slowly" and like him "beaten down and marred and wasted" until one is literally a mummy, encased in an ever shrinking, slowly contracting skin of steel, is a fate not pictured in any tragedy, ancient or modern.

Sir William Osler 1849-1919

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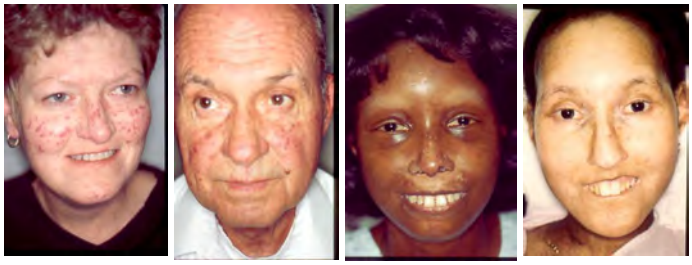
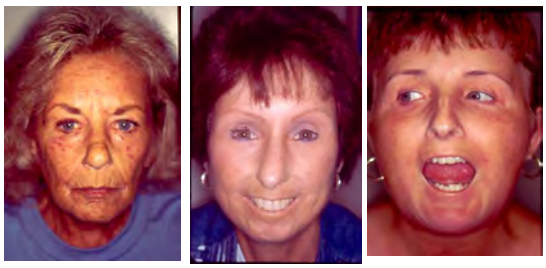


Various well defined subtypes of scleroderma exist with common clinical links but unique features, disease course and expression with different potential outcomes…



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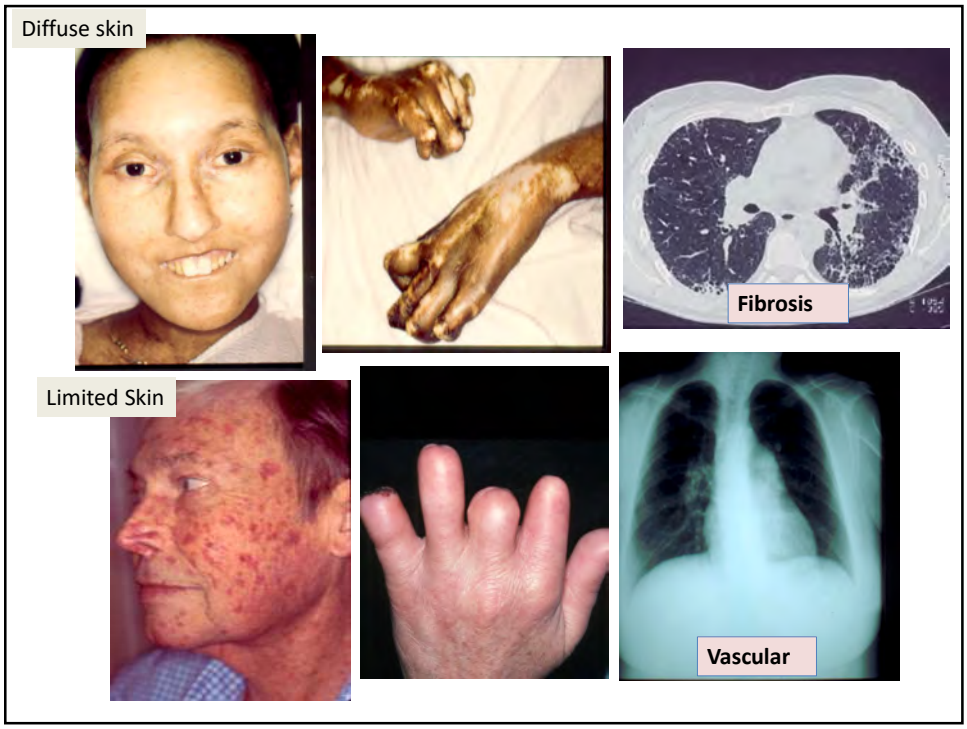

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Autoantibodies Predict Phenotype

Autoantibody	Cutaneous subtype	Other features
Centromere A/B/C	Limited skin/CREST	Ischemic digital loss PAH Overlap syndromes: Sjogren's, Hashimoto's, PBC
Topoisomerase-1 (Scl-70)	Diffuse>limited skin	ILD
RNA polymerase III	Rapid diffuse skin, contractures	Renal crisis Skeletal myopathy and cardiac disease GAVE

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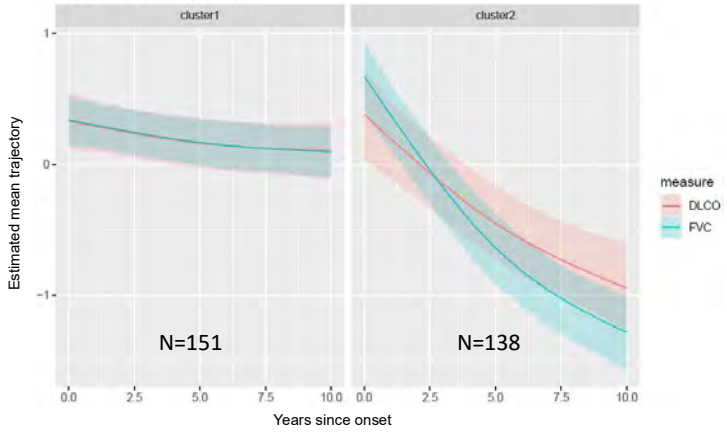
Heterogeneity within autoantibody subgroups

289 patients with SSc and anti-Topoisomerase 1 antibodies



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The challenge

- Heterogeneous disease; several distinct sub-phenotypes
  - Severe diffuse skin, renal crisis, cardiac and skeletal myopathy
  - Limited skin, telangiectasia, digital loss, pulmonary hypertension
- "15% rule"
  – Various complications occur in about 15% of patients (clinically significant ILD, PH, cardiac involvement, renal crisis, etc)
- Distinct autoantibodies strongly predict phenotype
- Relevant clinical events evolve over time
- Variability in treatment response

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Objectives

Part I – How can we address heterogeneity in SSc?

- Discuss a method for identifying clinically relevant subgroups in scleroderma
- Review an example from the study of cancer-induced autoimmunity in scleroderma

Part II – How can we broaden these approaches to further a goal of personalized medicine in rheumatic diseases?

- Propose a framework for generalizing this method across multiple parameters and outcomes

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An approach to neutralize complexity

- Use data from prospectively followed and measured patients to define clinically relevant and mechanistically anchored disease subgroups
- Perform progressive subgrouping to homogeneity
- Let's look at an example…

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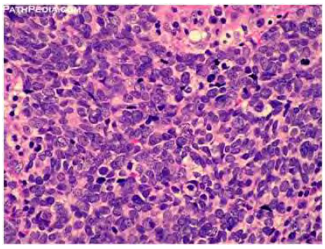
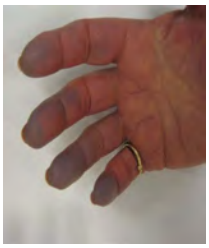
An initial case that lit the spark…

- 43 year old female (smoker) seen 9/2007
- 4/06 Raynaud's, swelling of hands and face
- During workup: **small cell carcinoma**





- Chemo (7/06), XRT (9/06), prophylactic brain XRT

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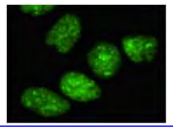
Within 1 year…

April 2007

- Raynaud's worsened
- Hands more swollen
- Rapid diffuse thickening involving entire body
- Thickening worse in radiation port: anterior chest, scapular region of back

Anti-RNA polymerase III positive



Denton CP. Case Studies in Systemic Sclerosis. 2011.

KEY QUESTIONS:

- Is scleroderma a by-product of an anti-tumor immune response?
- Could distinct autoantibodies be fingerprints of what is occurring at disease initiation?

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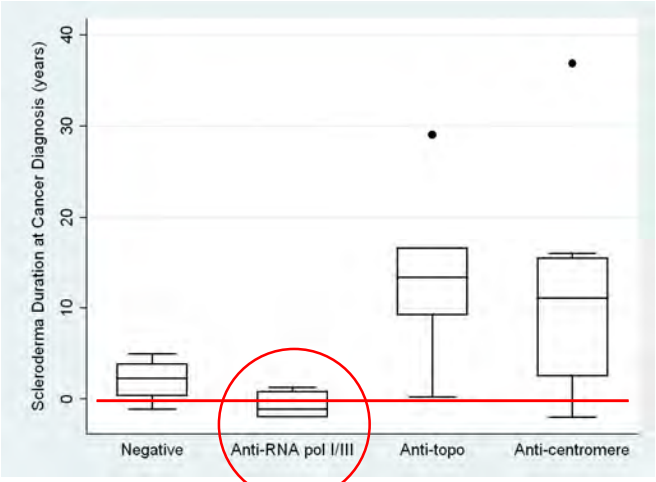
Anti-RNA polymerase III positive SSc: clustering of cancer with SSc onset



Anti-RNA polymerase III+ SSc patients: >5-fold increased risk of cancer within 2 years of SSc onset.

Findings validated in several SSc cohorts internationally.

Shah et al. Arthritis Rheum 2010
Shah et al. Arthritis Rheum 2015

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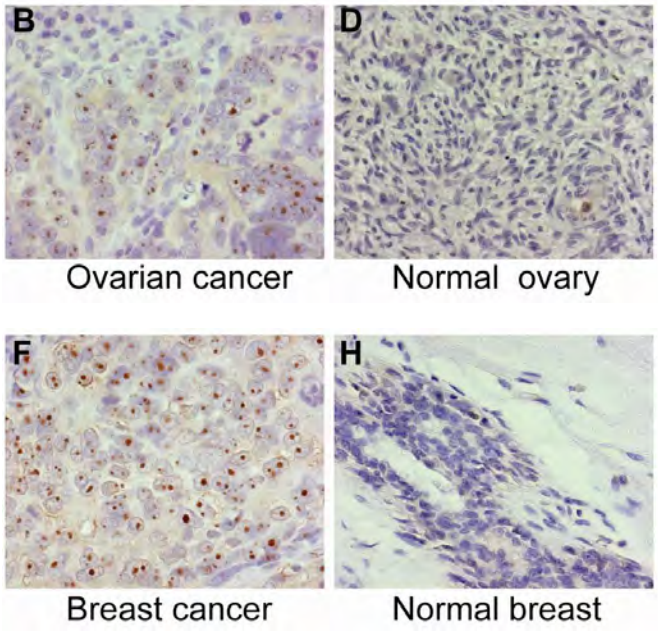
RNA Polymerase III Expression



Shah et al. Arthritis Rheum 2010

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International Validation

Article	Country (N)	Time interval	Key findings
Airo' (2011)	Italy (360)	-6 mos to +12 mos	↑ prevalence of cancer & cancer synchronous to SSc
Nikpour (2011)	Australia (451)	± 5 years	OR 4.2 (95% CI 1.3-13.4)
Moinzadeh (2014)	UK (2177)	± 3 years	OR 5.83 (95% CI 3.21-10.92)
Saigusa (2015)	Japan (261)	-6 mos to +12 mos	↑ prevalence of cancer & cancer synchronous to SSc
Lazzaroni (2017)	EUSTAR (357)*	-6 mos to +12 mos	↑ prevalence of cancer & cancer synchronous to SSc
Callejas-Moraga (2019)	Spain (221)*	± 5 years	Nonsig. ↑ in cancer synchronous to SSc
Morrisroe (2020)	Australia (1727)	± 5 years	OR 2.14 (1.03-4.45)

*Case-control study

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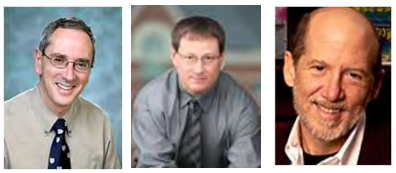
Does simultaneous scleroderma/cancer presentation plus highly specific immune response to POLR3/RPC1 provide the opportunity to understand any mechanistic relationship?



Joseph et al. Science 2014

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Features of 16 scleroderma patients with cancer

Patient #	Scleroderma duration at diagnosis of cancer (yrs)	Auto-antibodies to:	Age at diagnosis of cancer	Cancer Type
SCL-1	-0.2	RPC1	51	Breast cancer
SCL-2	-0.1	RPC1	42.3	Lung cancer
SCL-4	-0.4	RPC1	44	Ovarian cancer
SCL-13	0.3	RPC1	51	
SCL-35	-2	RPC1	50	
SCL-42	1.5	RPC1	47	
SCL-81	-4.2	RPC1	54.6	Colorectal cancer
SCL-82	2.5	RPC1	51.1	Breast cancer
SCL-5	9.2	TOP1	74.6	Lung cancer
SCL-8	0.4	TOP1	65.1	Breast cancer
SCL-11	13.4	TOP1	55.7	Breast cancer
SCL-12	34	CENPB	68.6	Anal cancer
SCL-19	34	TOP1	74.1	Breast cancer
SCL-24	36.9	CENPB	64.2	B cell lymphoma
SCL-32	-2.5	CENPB	43.1	Breast cancer
SCL-85	15	TOP1	52.1	Breast Cancer

Mutant and WT peptide-specific CD4+ T cells

75% of RPC1 patients have genetic abnormalities at that locus; this is not a feature of any patients with other antibodies ($p<0.05$) or cancers without scleroderma (COSMIC, $p<10^{-20}$)

Joseph et al. Science. 2014

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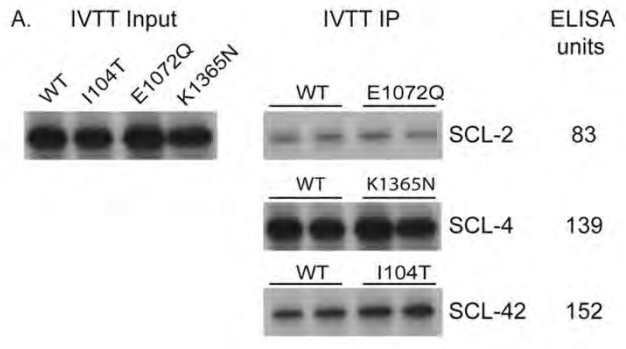
Autoantibodies do not discriminate between wild type and mutated proteins



Joseph et al. Science. 2014

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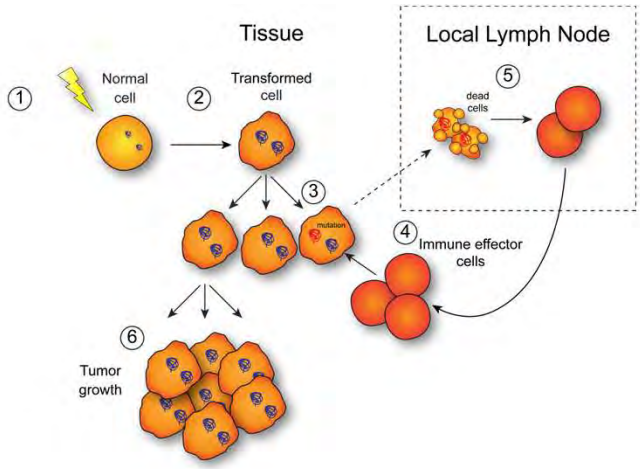
Mutated autoantigen in cancer induces an anti-tumor immune response



Shah et al. Arthritis Rheumatol. 2015

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Paraneoplastic Autoimmune Syndromes

Autoimmune Inflammatory Myopathies

- Dermatomyositis: adenocarcinomas

Neuro-degenerative Syndromes

- Cerebellar degeneration: Breast and ovarian
- Opsoclonus-myoclonus ataxia: Small cell lung, breast, ovarian

Vitiligo

- Vitiligo developing in patients with melanoma is associated with increased survival

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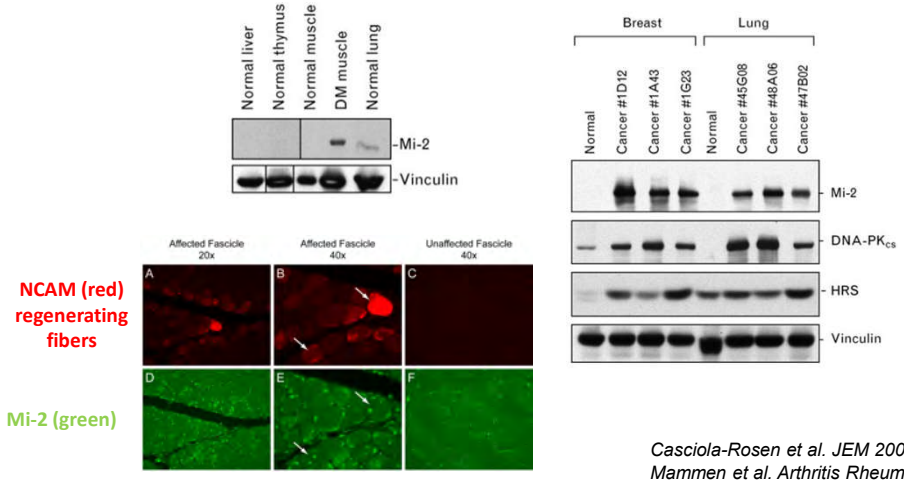
Myositis Autoantigens: Expressed in Cancers & Regenerating Muscle



Casciola-Rosen et al. JEM 2005
Mammen et al. Arthritis Rheum 2009

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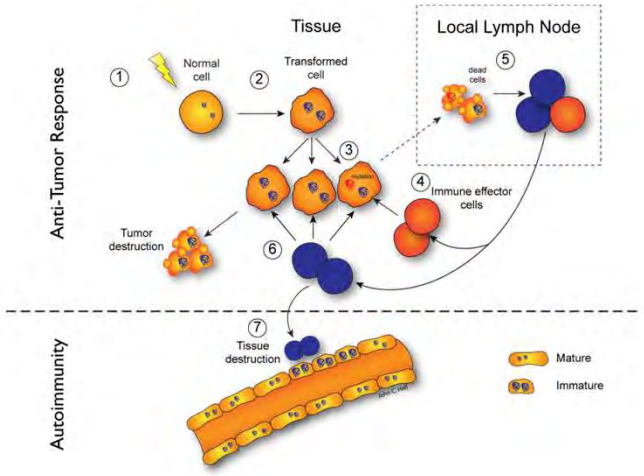
When immune response spreads to unmutated autoantigen, additional anti-cancer effect & damage of self tissues result



Shah et al. Arthritis Rheumatol. 2015

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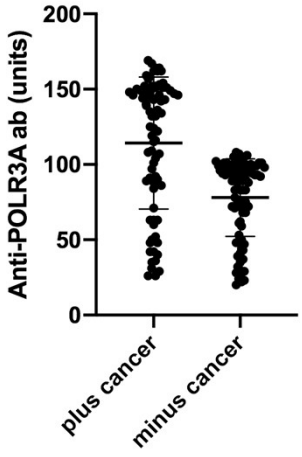
Are anti-POL3 antibody titers clinically informative?



High titer anti-POL3 (>110 U)
60% of cancer group
0% of no cancer group

Need malignancy workup

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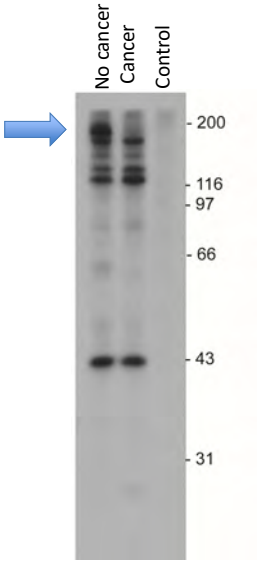
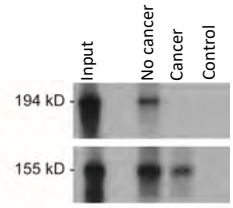
Are there other differences in the immune response in those without vs with cancer?



IVTT IP confirms new band is large subunit of RNA polymerase I



Immune response targeting POL3 & POL1 machinery = a cancer protective combination

Shah et al. A&R, 2019

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POL3 + POL1

- BMH21, a small molecule inhibitor of RNA polymerase I, has anti-tumor activity against multiple cancer cell lines in vitro as well as in animal models
- 18.2% of no cancer group vs 3.8% of the cancer group is anti-RPA194+ (p=0.003)
- Raise the important question of whether multiple orthogonal immune responses may have a more potent anti-cancer effect than immune responses with a narrower set of targets

Key point: Value in progressive subgrouping to homogeneity

Shah et al. A&R 2019

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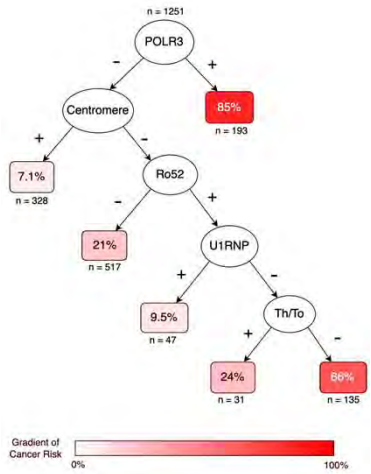
Combinations of immune responses may be powerful tools for cancer risk stratification



High risk:
-POLR3+
-Ro52+, U1RNP-, Th/To-

Intermediate risk:
-POLR3-, Centromere-, & Ro52-
-Ro52+ & Th/To+

Low risk:
-Centromere+
-Ro52+ & U1RNP+

Key point: Value in progressive subgrouping to homogeneity

Kim et al. Manuscript under review

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Timing of cancer diagnosis and SSc onset

If cancer could be trigger for SSc in distinct autoantibody subsets:

How should we screen for cancer in patients with new SSc?

Could we use autoantibodies, alone or in combination, as tools for cancer risk stratification?

Does cancer therapy = SSc therapy?

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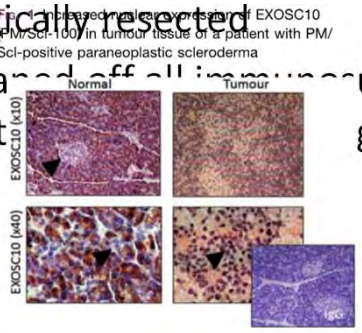
Cancer therapy = SSc therapy?

- 43 year old woman with diffuse SSc and polymyositis overlap, anti-PM/Scl+
- Solid pseudopapillary pancreatic neoplasm
- Cancer surgically resected
- Rapidly weaned off all immunosuppression with resolution of SSc and myositis



Bruni et al. Rheumatology. 2017

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The Unmet Need – A Clinician's Perspective

Cancer could be a trigger for SSc in these subsets, but we **lack clinically actionable metrics** to guide or inform:

- who we should screen for cancer
- when we should screen
- for what tumor types
- how we treat cancer and scleroderma when they coexist
- whether cancer therapy is effective scleroderma therapy

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Who is at risk, when, and for what?

- Compare cancer incidence in SSc to the general population: Surveillance, Epidemiology and End Results Program (SEER)
- Examine whether cancer risk overall and for specific cancer sites differs by:
  - Autoantibody subset
  - Cutaneous subset
  - Timing
- 2383 patients, 205 cancers

Igusa et al. ARD 2018

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Study population

- 2383 patients contributing 37,686 person years
- 205 cancers by end of f/u
- Mean age SSc onset 42.4 ± 15.1 yrs
- 60% limited SSc
- 83% female
- 76% self-identified as white race

Autoantibody status

Centromere, N=608

Topo, N=481

Pol 3, N=278

CTP-negative, N=379

Not classifiable, N=671

Igusa et al. ARD 2018

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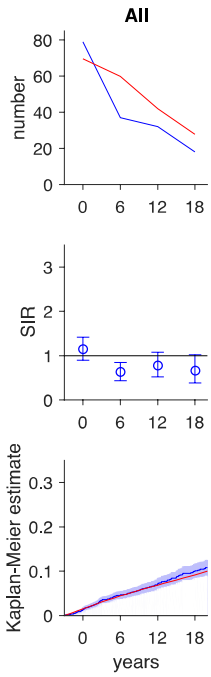

Igusa et al. Ann Rheum Dis, 2018

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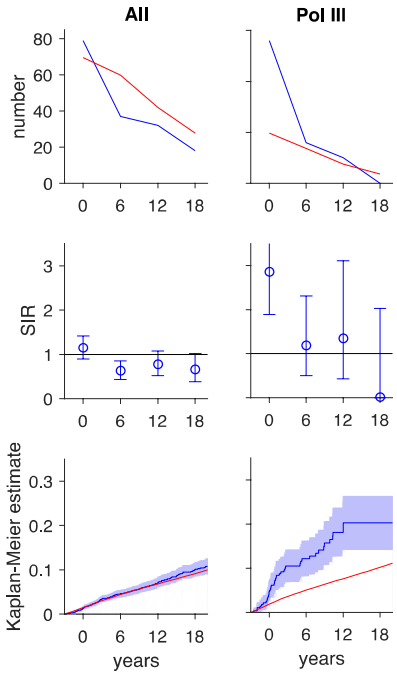

Igusa et al. Ann Rheum Dis, 2018

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Risk within 3 years of SSc onset

Anti-POLR3 – SIR 2.84 (95% CI 1.89-4.10)

Subtype	Cancer site	SIR	95% CI
Diffuse	Breast	5.1	2.7-9.0
	Prostate	7.2	2.0-18.4
	Tongue	43.9	5.3-158.5
Limited	Lung	10.4	1.3-37.7

Igusa et al. Ann Rheum Dis, 2018

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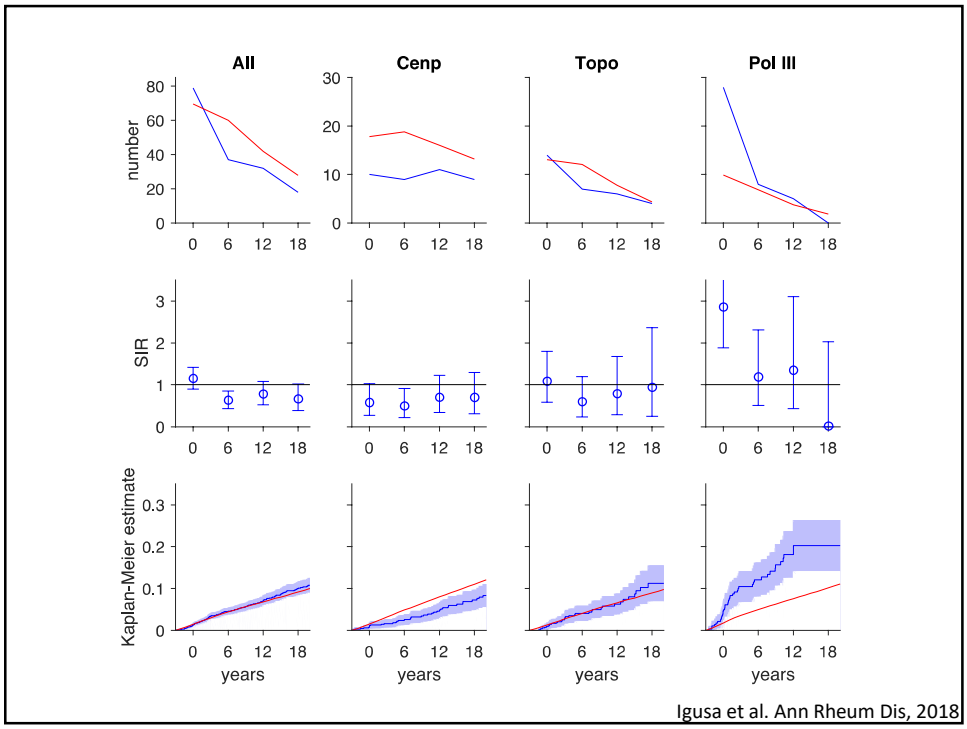
All
Cenp
Topo
Pol III
number
SIR
Kaplan-Meier estimate
years
Igusa et al. Ann Rheum Dis, 2018

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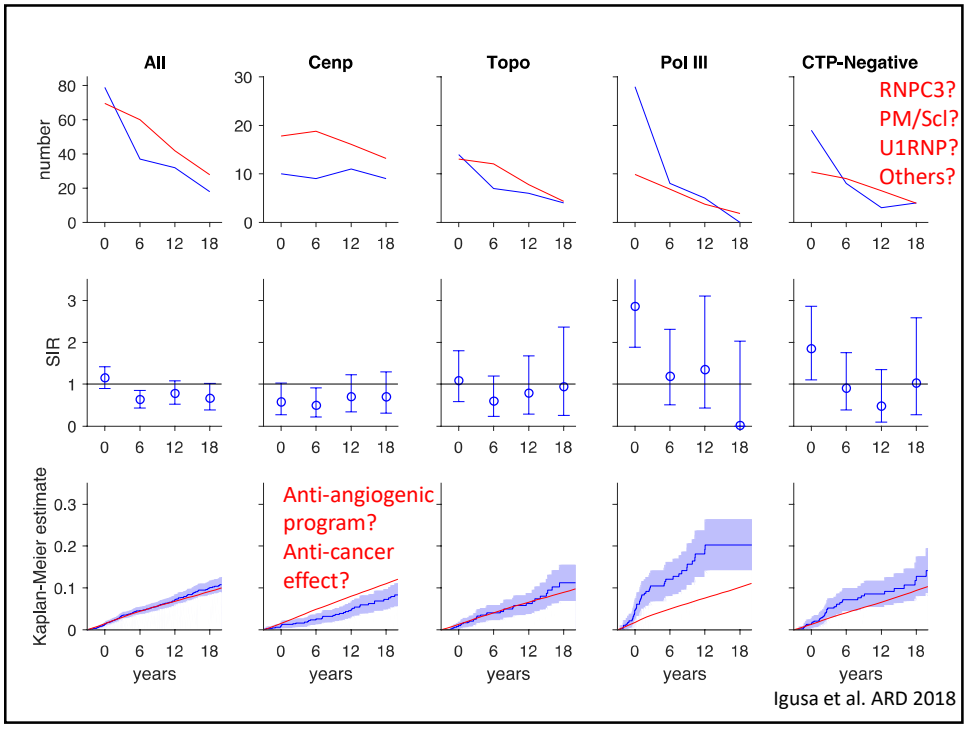
All
Cenp
Topo
Pol III
CTP-Negative
RNPC3?
PM/Scl?
U1RNP?
Others?
number
SIR
Kaplan-Meier estimate
Anti-angiogenic program?
Anti-cancer effect?
years
Igusa et al. ARD 2018

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Conclusions: subsetting cancer risk

- Close temporal relationship between cancer and SSc onset among SSc patients with anti-RNA polymerase III
- Compelling biologic data suggest a model of cancer-induced autoimmunity in POL positive patients
- Anti-CENP is associated with a striking decrease in cancer risk; unique combinations of immune responses may be cancer protective
- Autoantibody and phenotypic subsets may define cancer risk and type in SSc
- Testing of novel liquid biopsy techniques and imaging measures (breast MRI & PET/CT) underway in high risk subgroups

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Conclusions - 2: application to other rheumatic diseases

- These key principles are shared between SSc and DM:
  - High cancer risk around time of disease onset
  - Risk highest in distinct autoantibody subsets
  - Genes encoding autoantigens are mutated in cancers and may induce the immune response
  - Disease course may parallel the course of the cancer
  - Preliminary data suggest that cancer screening could be targeted by autoantibody type and clinical features.
- Combinations of immune responses may associate with "cancer protection" – SLE breast cancer example

# of autoantibodies	SLE cohort SIR (95% CI)	p-value
0-2	0.84 (0.47-1.39)	0.60
3+	0.41 (0.16-0.84)	0.01

Shah et al. ART 2021

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An approach to neutralize complexity

Key lessons learned from studying cancer in scleroderma:

- The approach used to recognize clinically relevant subgroups – cancer + specific immune response + trajectory over time – can be generalized.
- This approach is measurement agnostic – and subgroup detection is powerful if you use orthogonal measures and look for coincidence in time and space.

Now how can we do this, for many outcomes, ***at scale****?*

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Objectives

Part I – How can we address heterogeneity in SSc?

- Discuss a method for identifying clinically relevant subgroups in scleroderma
- Review an example from the study of cancer-induced autoimmunity in scleroderma

Part II – How can we broaden these approaches to further a goal of personalized medicine in rheumatic diseases?

- Propose a framework for generalizing this method across multiple parameters and outcomes

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Johns Hopkins Precision Medicine Initiative

JOHNS HOPKINS inhealth

*in*Health is using revolutionary tools of measurement, data science, and connectivity to discover clinically-relevant and biologically-anchored subgroups at scale, and to deliver what we learn to impact the precision and value of health care

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The Discovery-Delivery Cycle

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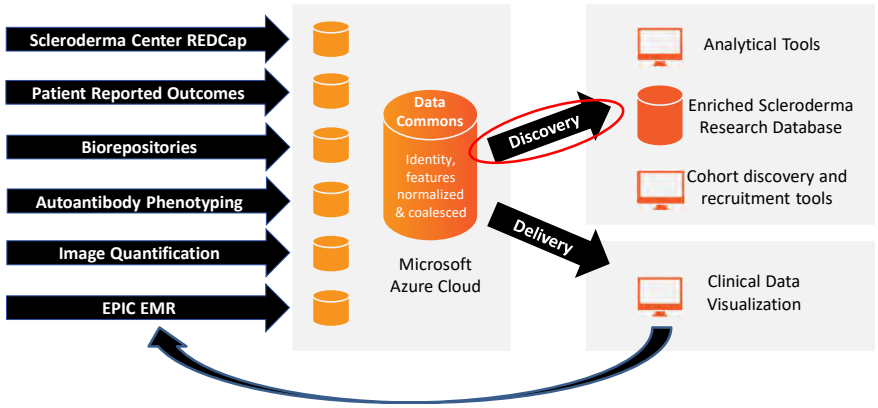
Discovery-Delivery Data Flow



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An approach to neutralize complexity… **at scale**

Our modified approach through the Precision Medicine Initiative:

- Set up a framework that offers the ability to look at multiple connections, links orthogonal datasets/measurements
- Recognize that more than one measurement likely predicts a patient's outcome and trajectory better than a single measurement
- Utilize new computational tools to identify subgroups and test their clinical/biological relevance

Goal of the PMAP Discovery Platform

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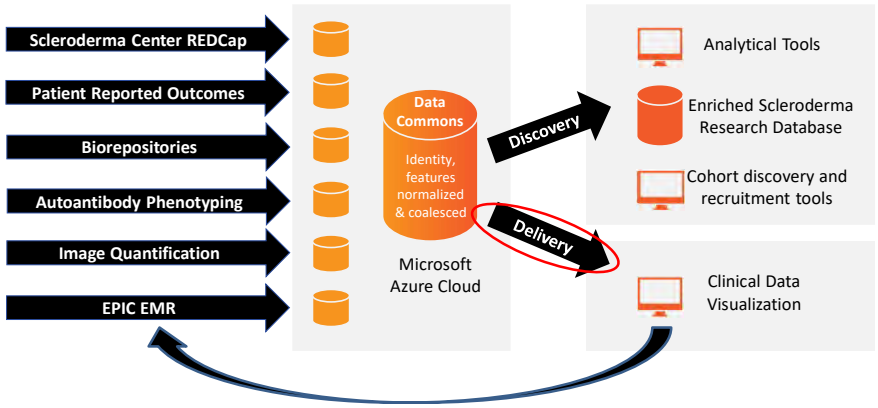
Discovery-Delivery Data Flow



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Medical decision making in a heterogenous disease

- Medical providers use cognitive skills to
  - Integrate information across multiple parameters and organ systems
  - Account for a patient's prior trajectory
  - Adjust for baseline risk factors (mental subgrouping)
- This results in an "estimate" of a patient's health state, risk for complications and need for high-risk therapies.
- This is informed by a provider's prior experiences caring for patients with a similar expression of disease → **not a generalizable process**, especially in a rare disease.

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How can we improve decision making?

- Can we harness knowledge gained from seeing a large population of patients with a rare disease to improve pattern recognition and risk estimation?
- Can we do this efficiently, at the point of care, and at the individual patient level?
- Can we better address questions that are meaningful to our patients?
  - What is the state of my disease?
  - What is my long term prognosis or trajectory?
  - How do I compare to other patients with scleroderma?

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Developing tools for individualized health

1. Patient Insight visualization tool
   - Illustrates an individual's trajectory across multiple organ systems
   - Synthesizes data from multiple sources
   - Interactive – can show trajectory relative to a population or a subgroup of interest
   - Web based API – to enable future dissemination
2. Computing personalized risk estimates for multiple complications
   - *Harness an individual patient's prior data AND the data of the population and subgroup to improve prediction of future trajectory*
3. Bringing individualized predictive modeling into the tool

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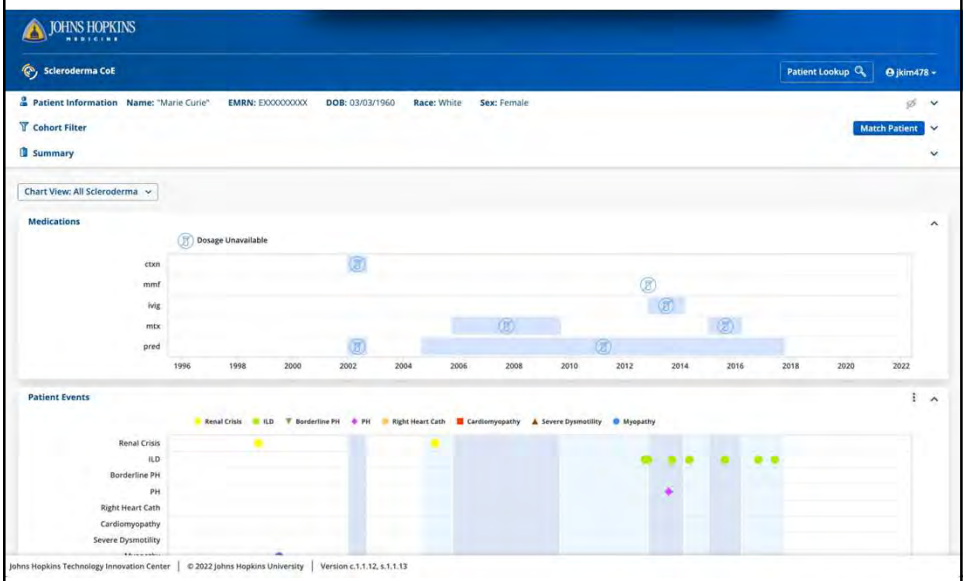

Patient Insight: Longitudinal Viewer

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Is this useful to patients and providers?

- Qualitative study with patients
  - Showing patients their own longitudinal trends
  - Illustrating individual data relative to other patients
- Rheumatology case assessments comparing Epic vs Patient Insight
  - Does immunosuppressive therapy need to be initiated or changed for ILD?
  - Should invasive testing be pursued to assess for pulmonary hypertension?

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Engaged and empowered patients

- *"It gave me a sense of my own disease severity and more perspective on that."*
- *"I am a very visual person, so seeing a graph is very helpful to me. If you would have just told me, I might have forgotten some of what you said, but now I can remember what those graphs look like."*
- *"With knowledge and understanding anything come things that I can be doing to better help myself."*
- *"I feel the more knowledge I have about my disease, the more confidence I have. When you have more confidence, you're more in control of the situation."*

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Highly efficient, data driven decision-making

- Rheumatologists looked at **~7.5-10.7x more data in ~80% of the time** when using Patient Insight compared to the EMR.
- Rheumatologists who recommended a change in the plan for testing or treatment reported **higher levels of confidence** in their decision.

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Happy clinicians

- *"It's nice to see everything laid out, like all organ systems. Usually, you just forget, even if it's your own patient, so I'd have to go back to first notes. But in this tool, I can pull it up in milliseconds."*
- *"I felt like I was better able to assess the scope of their disease not only in the recent months, but from onset, which is really cool."*
- *"I'm very confident [because] the tool allowed me to refine my diagnosis based on the data provided."*

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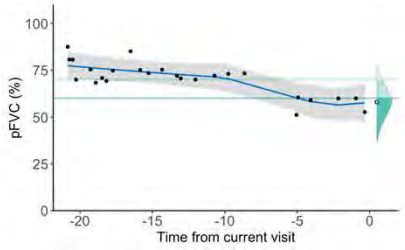
Bayesian multivariate linear mixed effects models

- Calculate $p(E)$ at time $j+$ using $Y_{ij+}|Y_i = y_i \sim N\left(E(Y_{ij+}|Y_i = y_i), Var(Y_{ij+}|Y_i = y_i)\right)$



	Estimated Risk
pFVC > 70	6%
60 < pFVC <= 70	34%
pFVC <= 60	59%

- Simultaneously characterize each patient's trajectory in multiple organs, from which the probabilities of the critical events are calculated
- Adjust for key population risk factors
- Harness information from data in other measures and from other patients to improve prediction
- Cross Validated Sequential Prediction (CVSP) algorithm
  - Updated risk predictions obtained without refitting the model by using a K-fold cross-validation method
  - Real-time predictions can be made as additional data are observed during a patient's visit

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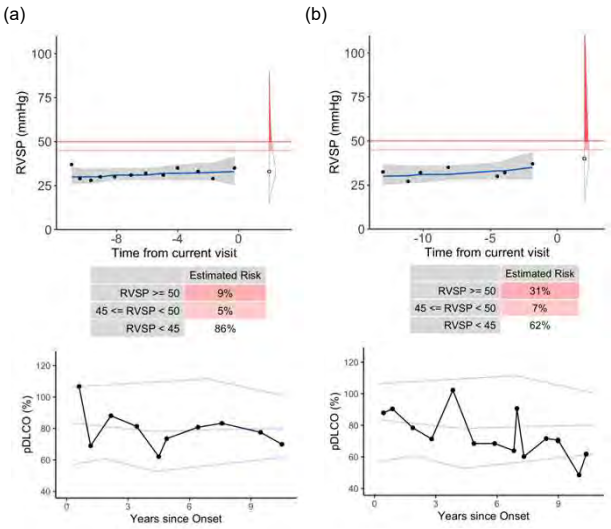
51 and 55 y.o. women, white race, diffuse cutaneous disease, negative for ACA, topo, POLR3



Patient (b) with subsequent cath-confirmed PAH

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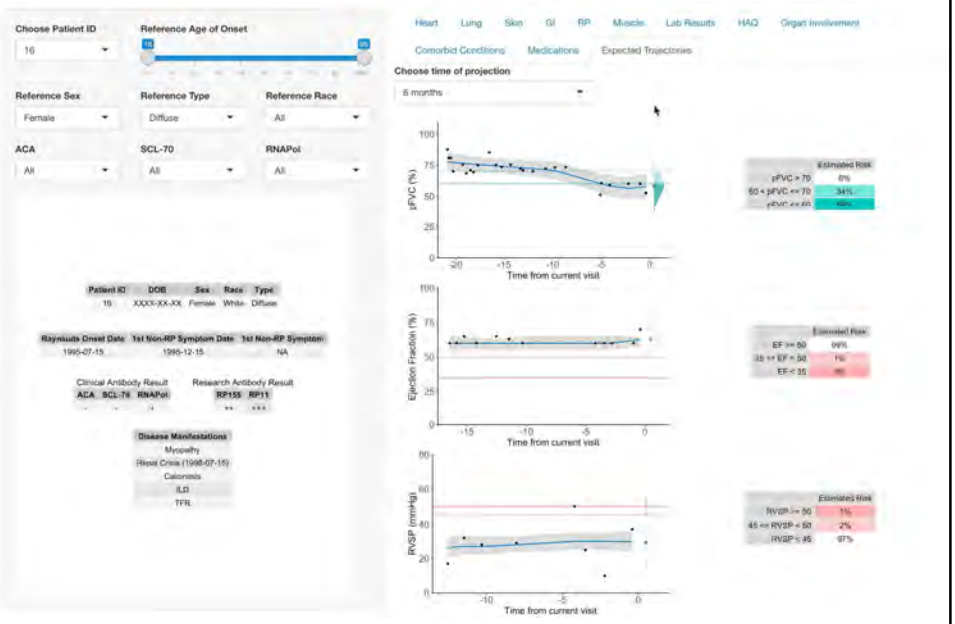

R Shiny App

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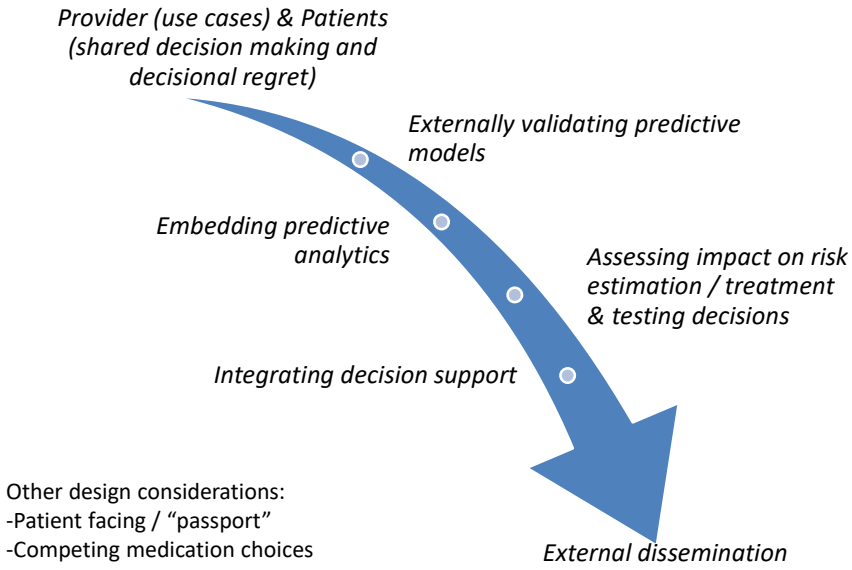
Is this valuable?



Other design considerations:
-Patient facing / "passport"
-Competing medication choices

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Personalized Medicine in Scleroderma

Approach: Utilize high dimensional data from prospectively followed patients and new computational tools to neutralize complexity and discover clinically relevant & biologically anchored subgroups

Vision:

- Gain insight into disease pathogenesis
- Identify patient subsets at high risk of complications
  - At an earlier stage of disease using novel biomarker, imaging, and ambulatory device monitoring strategies
- Define which subgroups are most likely to benefit from different screening & therapeutic approaches
- Develop an individual level predictive model of a patient's likely trajectory
- Assess whether these measures improve patient outcomes, reduce costs, and can be translated to other settings

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Many people have enabled this work

Cancer & Scleroderma:
Antony Rosen
Livia Casciola-Rosen
Fredrick Wigley
Laura Hummers
Takeru Igusa
Kala Visvanathan
Marikki Laiho
Chris Mecoli
Laura Cappelli
Rosen Lab
Bert Vogelstein, Ken Kinzler & lab
Rheumatic Disease Research Core Center
Scleroderma Center Faculty & Staff

Precision Medicine:
Scott Zeger
Ji Soo Kim
Adrianne Woods
Rob Smithwright
John Scott
Thomas Grader Beck
Aalok Shah
Lauren Smith
Lauren Fisher
Ana-Maria Orbai
Diane Koher
Megan Singleton
Scott Carey

Funding Sources:

JHU inHealth and PMAP initiatives

NIH/NIAMS: R01 AR073208, K24 AR080217, P30 AR070254
Scleroderma Research Foundation
Stabler Foundation
Chresanthe Staurulakis Memorial Fund
Jerome L. Greene Foundation
Ira T. Fine Discovery Fund
Bechtle Precision Medicine Fund

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