ASCPT 2022 NETWORK & COMMUNITY EXPERIENCE

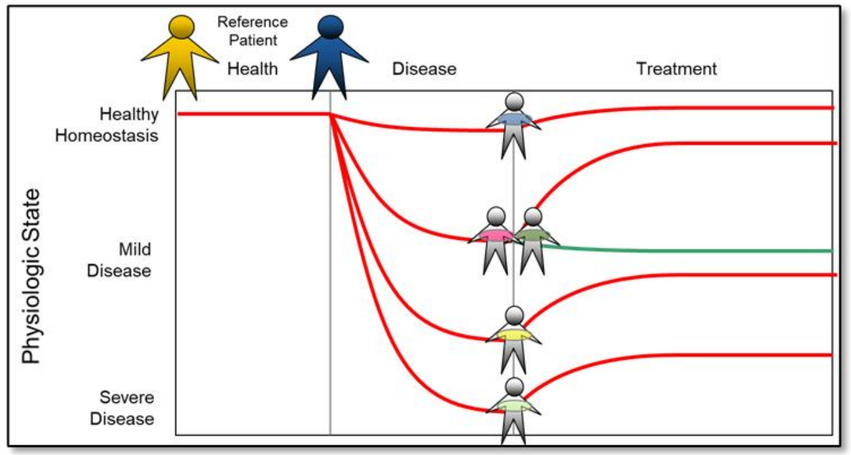
DISRUPTIVE INNOVATION

ASCPT American Society for Clinical Pharmacology & Therapeutics

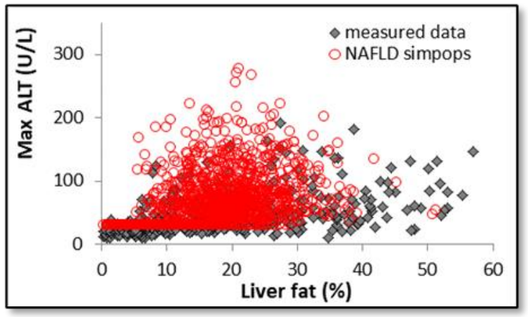
Scott Q Siler

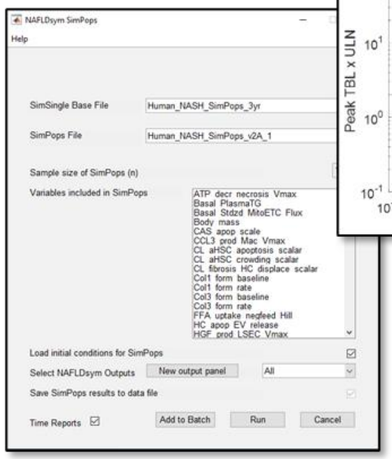
Capturing Interpatient Variability with SimPops

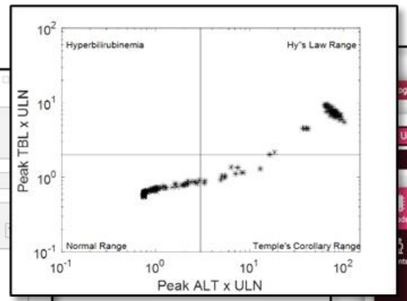
SimPops Provide Significant Value for Drug Development

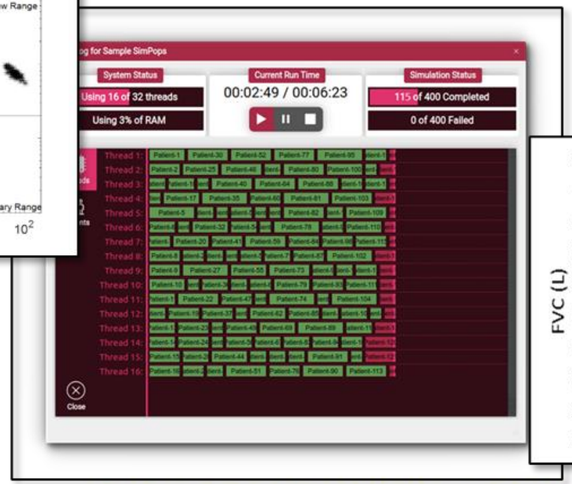


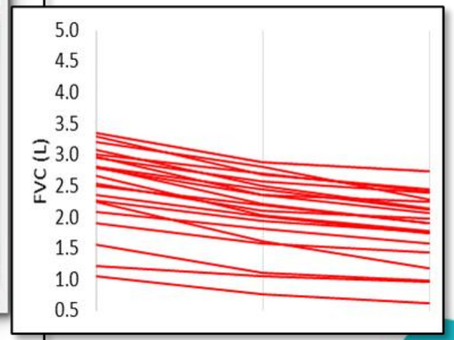
"The SimPops are the Crown Jewel"





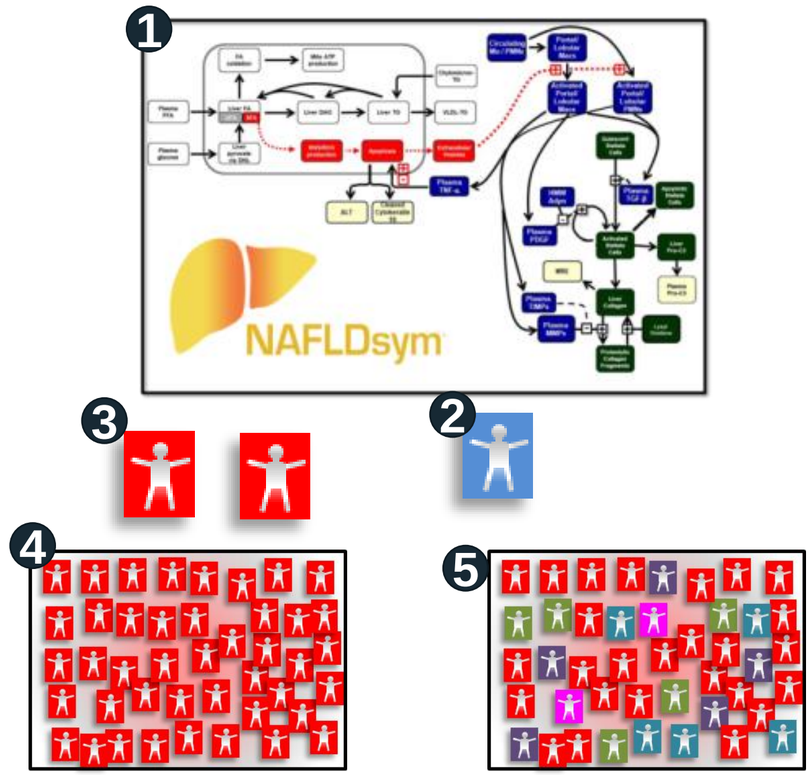




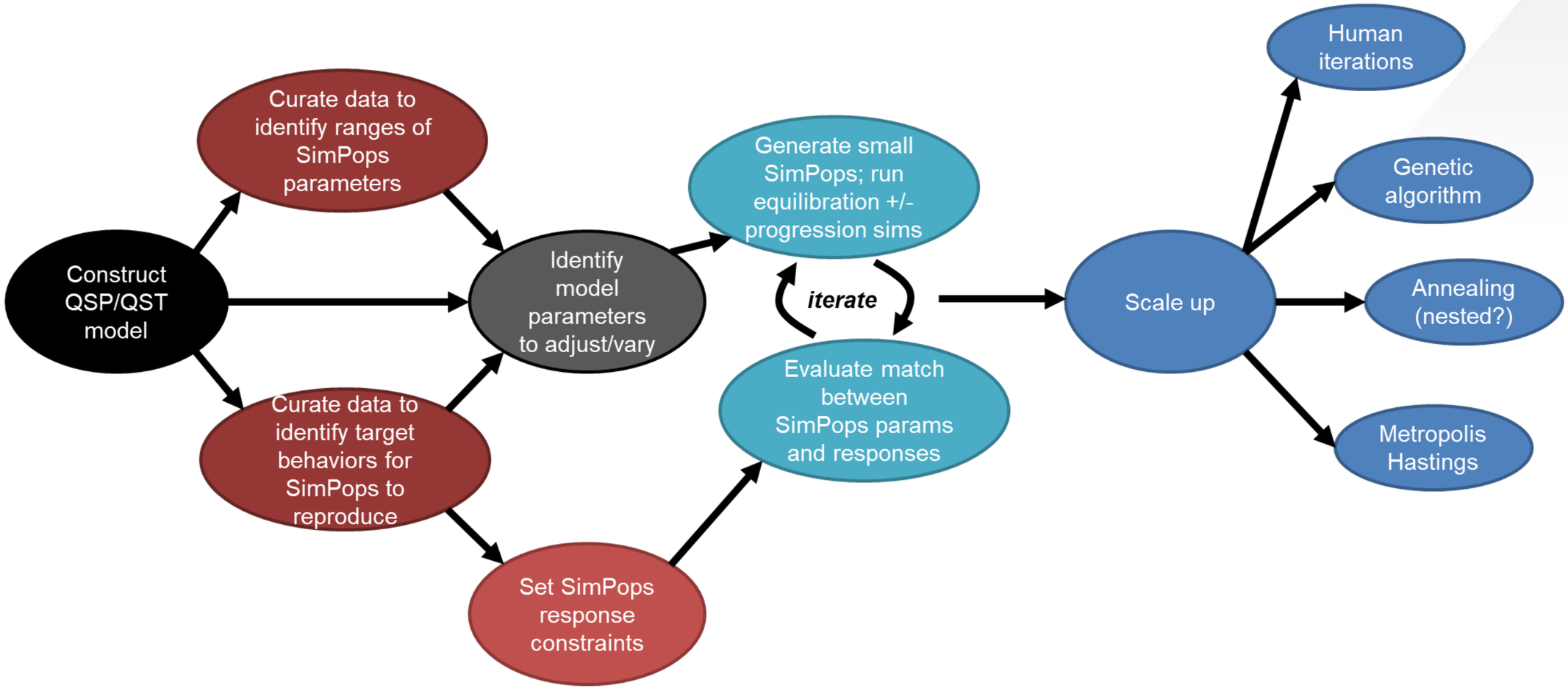


General Process for Generating SimPops

1. Construct mechanistic QSP/QST model
2. Baseline parameters represent healthy simulated patient (AKA virtual patient)
3. Adjust specific parameters representing key pathophysiologic processes to generate a few representative simulated disease patients
4. Vary and combine pathophysiologic parameters across ranges to generate a simulated population SimPops (AKA Virtual Population)
5. Characterize and validate SimPops by comparing with data and treating with standard-of-care treatments



General SimPops Development Workflow

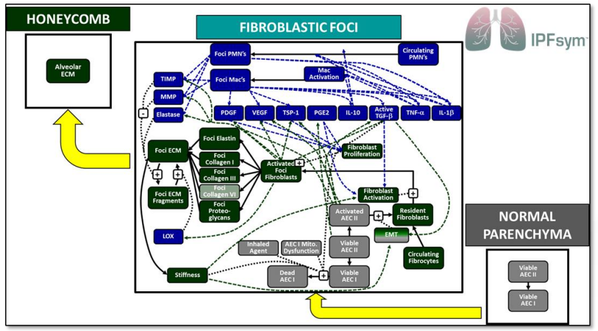


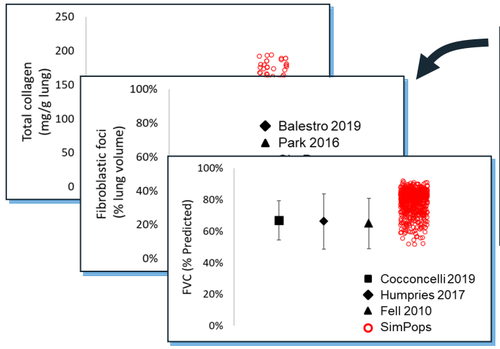
DILIsym Services QSP/QST Models

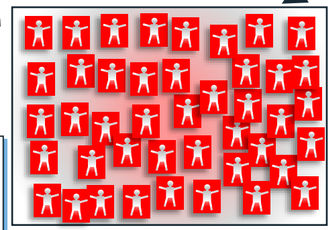
	Model	Disease area	Key References	Primary biomarkers included:	Number of compounds/ targets evaluated
QSP	NAFLDsym	Non Alcoholic Fatty Liver Disease and Non Alcoholic Steatohepatitis	Kenz 2020, Kenz 2019, Longo 2018, Siler 2018	Histologic NAS, histologic fibrosis score Liver fat (MRI), plasma ALT	20-25
QSP	IPFsym	Idiopathic pulmonary fibrosis	Siler 2021	Forced vital capacity; high resolution computed tomography	6
QSP	ILDsym (*in progress*)	Interstitial lung disease	--	Forced vital capacity; high resolution computed tomography	5 (*by end of 2021*)
QSP	CARDIOsym	Cardiac recovery following myocardial infarction	Kenz 2021	Cardiomyocytes, myofibroblasts, collagen	2
QSP	KIDNEYsym (*in progress*)	Kidney duresis	--	Urine volume; urinary sodium loss	3 (*by end of 2021*)
QSP	MITOsym	Hepatocyte bioenergetics	Yang 2015	Oxygen consumption rate; ATP concentrations	>70
QST	DILIsym	Drug induced liver injury	Shoda 2017, Battista 2020, Eichenbaum 2020	Plasma ALT, plasma AST, plasma bilirubin	>70
QST	RENAsym	Drug induced kidney injury	Gebremichael 2020	Urine KIM-1, urine αGST, serum creatinine	10 (*by end of 2021*)

Pathophysiologic Variability Represented in IPFsym SimPops

- SimPops are population samples with variability across key areas of IPF pathophysiology
- Multiple parameters are varied to produce diverse possible simulated patients
- Simulated patients are compared with a multitude of clinical data to validate pathophysiology within model
- Response data (e.g., nintedanib/pirfenidone) used to further validate the SimPops





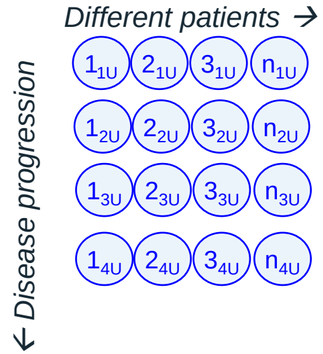
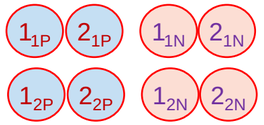


Variables Used to Construct the IPFsym v1A SimPops
Height
Age
AEC apoptosis rates
Immune cell recruitment and activation
Inflammatory mediator production
Fibroblast activation and proliferation
ECM synthesis and degradation
Collagen cross linking and ECM stiffness
EMT (exploratory)
Progression rates

SimPops Patient Parameter Selection

Parameter	baseline	SD	Mean	Max	Min	Upper SD	Lower SD	Distrib	
age	30	8.9	65	85	50	8.9	3	Norm	
Gender	1	0.2	1.31	2	1	0.2	0.2	Binom	
Body_mass	70	14.5	78	110	55	14.5	14.5	Norm	
initial_frac_ff	0.22	0.03	0.1	0.45	0.01	0.1	0.05	Norm	
initial_frac_honeycomb	0.085	0.017	0.05	0.45	0.01	0.05	0.02	Norm	
TGF_AEC_I_apop_Vmax	0.000586568	0.000167172	0.000588784	0.00092	0.000125	0.00025	0.000167172	Norm	covariate
TNF_AEC_I_apop_Vmax	0.002281258	0.000650159	0.002286929	0.003611	0.000989	0.000650159	0.000650159	Norm	covariate
TGF_AEC_II_apop_Vmax	0.000697932	0.000198911	0.000692378	0.0011	0.0003	0.0002	0.0002	Norm	covariate
TNF_AEC_II_apop_Vmax	0.000932318	0.000265711	0.000924494	0.001463742	0.000400898	0.000265711	0.000265711	Norm	covariate
prolif_signal_Vmax	105.8103211	31.74309634	116.3518633	169.29648	95	31.74309634	5	Norm	
activation_factor	0.742029952	0.5	1.65	2.6	0.7	0.5	0.5	Uniform	
active_apop_rate	0.0000809	0.00002427	8.0773E-05	0.00012944	0.00003236	0.00002427	0.00002427	Norm	
MMP_prod_fblast_Vmax	8.835152737	1.767030547	8.761725035	20	4	3	1.767030547	Norm	
TGF_prod_Mac_res_Vmax	250	50	253.1419175	375	125	50	50	Norm	
TGF_prod_Mac_recr_Vmax	130	26	130	195	65	26	26	Norm	
TGF_prod_AECII_Vmax	250	50	250	375	125	50	50	Norm	
TGF_prod_fblast_Vmax	130	26	130	195	65	26	26	Norm	
PDGF_prod_fblast_Vmax	33522	6704.4	33264.03625	50283	16761	6704.4	6704.4	Norm	
VEGF_prod_fblast_Vmax	1359.754074	271.9508148	1367.978015	2039.631111	679.877037	271.9508148	271.9508148	Norm	
TNF_prod_Mac_res_Vmax	1004.5	200.9	994.3850553	1506.75	502.25	200.9	200.9	Norm	
TNF_prod_Mac_recr_Vmax	2009	401.8	2031.019551	3013.5	1004.5	401.8	401.8	Norm	
NE_prod_neut_Vmax	138486	27697.2	138068.3047	207729	69243	27697.2	27697.2	Norm	
RFb_act_Vmax	0.005	0.001	0.01	0.03	0.005	0.004	0.002	Norm	
LOX_prod_Vmax	30000000	6000000	29649892.12	45000000	15000000	6000000	6000000	Norm	
LOX_half_life	1	0.2	1.00823194	1.5	0.5	0.2	0.2	Norm	
Procol1_synth_baseline	0.1268	0.02536	0.124652886	0.20288	0.07608	0.04	0.02536	Norm	covariate
Procol3_synth_baseline	0.1106	0.02212	0.110164252	0.1659	0.0553	0.02212	0.02212	Norm	covariate
Elastin_synth_baseline	0.1071	0.02142	0.107714105	0.16065	0.05355	0.02142	0.02142	Norm	
Proteoglycan_synth_baseline	0.018	0.0036	0.018008191	0.027	0.009	0.0036	0.0036	Norm	
Procol1_prod_act_fibroblast	0.0006	0.0001	0.0006009	0.001	0.00025	0.0001	0.0001	Norm	covariate
Procol3_prod_act_fibroblast	0.0006	0.0001	0.000602962	0.001	0.00025	0.0001	0.0001	Norm	covariate
Elastin_prod_act_fibroblast	0.005	0.001	0.005417601	0.0075	0.0025	0.001	0.001	Norm	
Proteoglycan_prod_act_fibrob last	0.00005	0.00001	5.00099E-05	0.000075	0.000025	0.00001	0.00001	Norm	
PDGF_AFb_prolif_Vmax	0.0015	0.0003	0.001495739	0.00225	0.00075	0.0003	0.0003	Norm	
VEGF_AFb_prolif_Vmax	0.0015	0.0003	0.001497669	0.00225	0.00075	0.0003	0.0003	Norm	
TGF_AEC_flow_Vmax	0.001	0.00005	0.0003	0.0005	0.00001	0.00005	0.00005	Norm	
Honeycomb_growth_rate	0.0000001	0.00000005	0.0000003	0.0000005	0.00000002	0.00000005	0.00000005	Norm	

Use of Different Categories of SimPops in IPFsym

Steady state	Disease progression With varying trajectories, location in progression trajectory	Disease progression + standards of care with different location in progression/ treatment trajectory
		
Use for exploration of disease progression	*Use to select cohorts with varying progression trajectories, location in progression spectrum while untreated*	*Use to select cohorts with varying progression trajectories, location in progression spectrum while on treatment*

Data to Support Evaluation of IPF SimPops

AEC

- Viable AECI and AECII numbers in fibroblastic foci and normal parenchyma

Immune

- Immune cells in fibroblastic foci
- Circulating mediators

Fibrosis

- Fibroblast numbers in fibroblastic foci
- Total collagen, elastin, proteoglycan (ECM) quantities in fibroblastic foci and/or honeycombed region
- Circulating Pro-C3 and lysyl oxidase-L2
- Stiffness in fibroblastic foci and honeycombed region

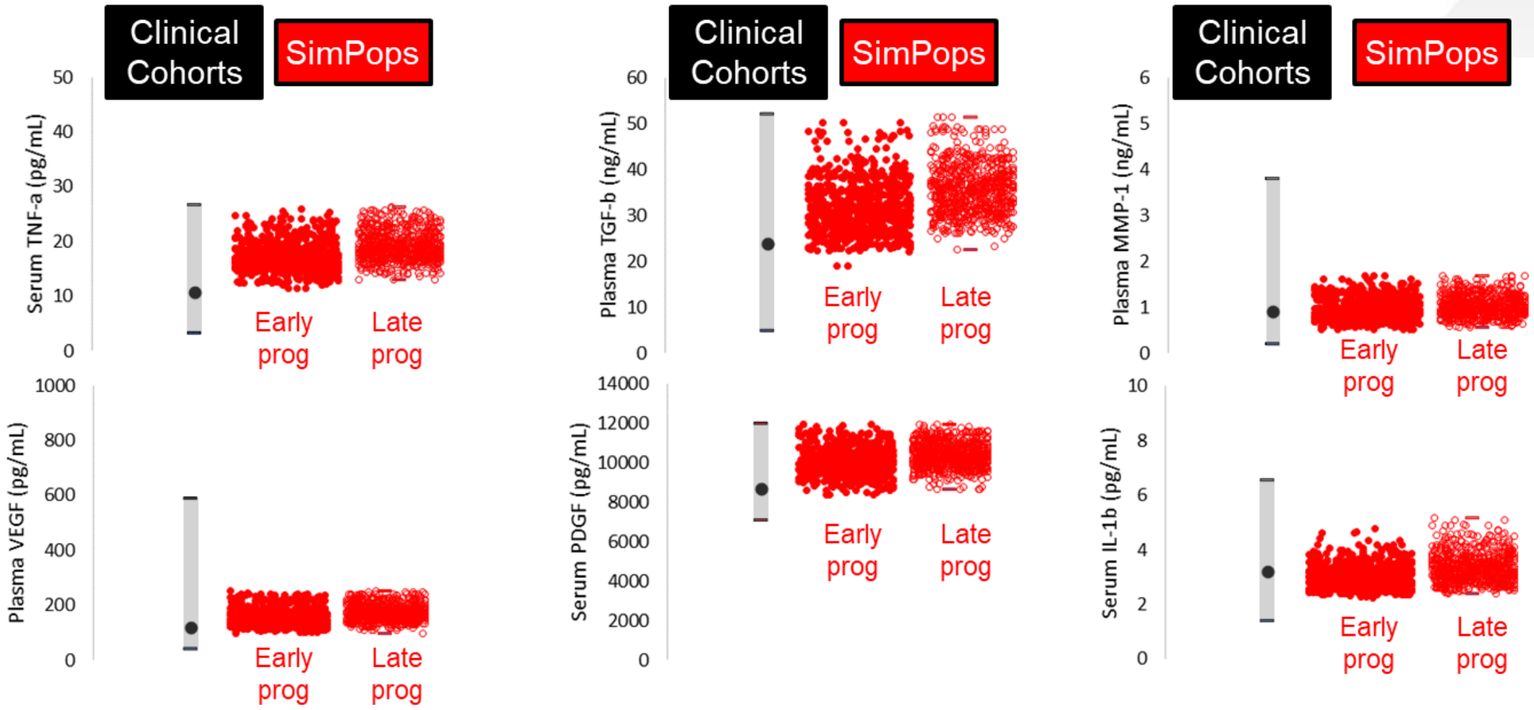
Clinical

- HRCT determination of honeycombing and fibroblastic foci volumes
- FVC, % predicted FVC in placebo and treated patients
- D_{LCO}, % predicted D_{LCO} in placebo and treated patients
- 6 minute walk distance in placebo and treated patients

Comparisons with clinical data made simultaneously across all axes

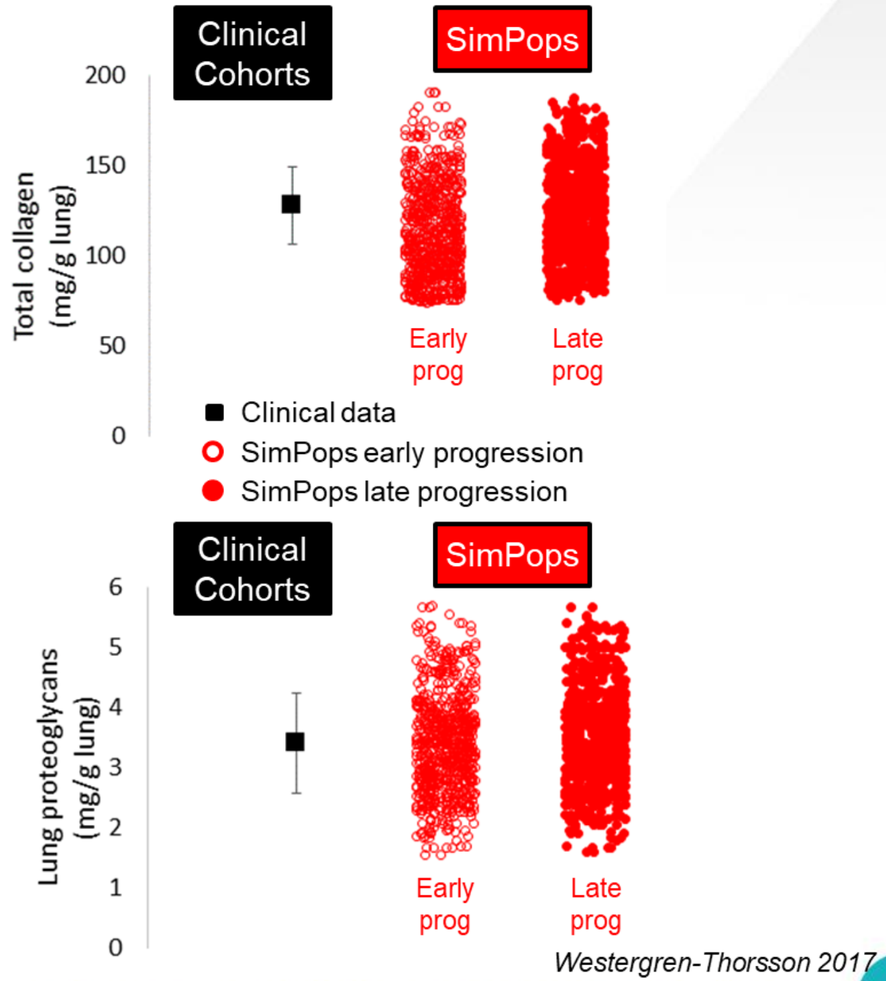
SimPops Mediator Levels Are Consistent with Clinical IPF Data

- Simulated mediators from preliminary SimPops are consistent with clinical data
  - Mean (•), minimum (-), maximum (-) plotted
  - Clinical data come from variety of sources
  - Other mediators (IL-10, TIMP-1, TSP-1, neutrophil elastase, LOX) also evaluated (*not shown*)



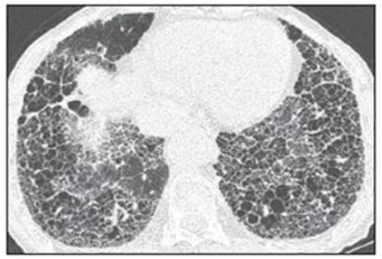
Simulated ECM Levels for SimPops Are Consistent with Clinical IPF Data

- SimPops patients (n=716) include varying degrees of IPF severity
  - Includes simulated patients early in progression and later in progression
  - All simulated patients survive 4 years of simulated disease progression
- Simulated lung collagen and proteoglycans are consistent with range of clinical data
  - Clinical data measured from lung biopsy and postmortem samples reported in Westergren-Thorsson 2017



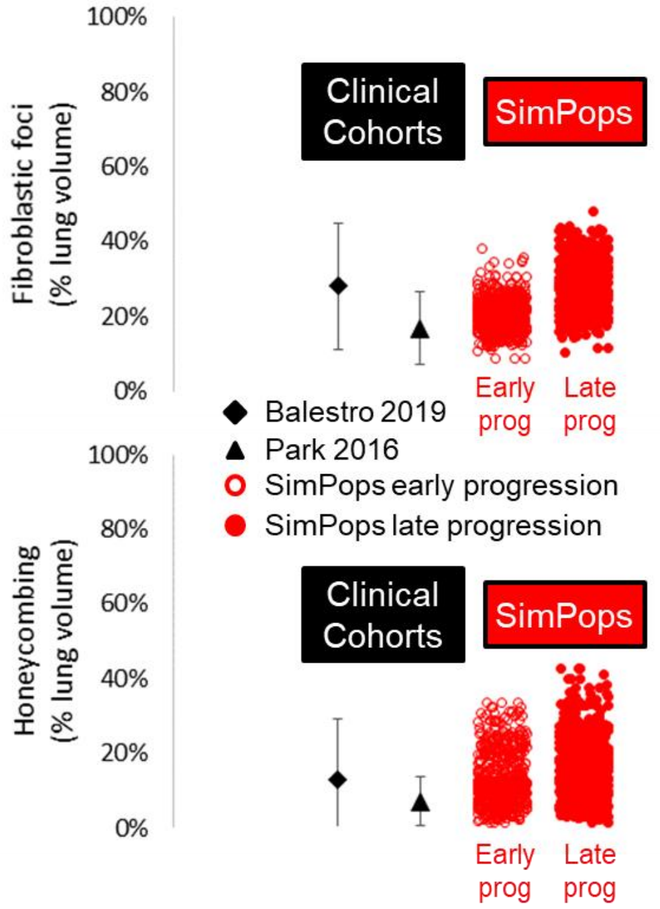
Westergren-Thorsson 2017

Simulated Fibroblastic Foci and Honeycombing for SimPops Are Consistent with Clinical HRCT Data



Park 2016

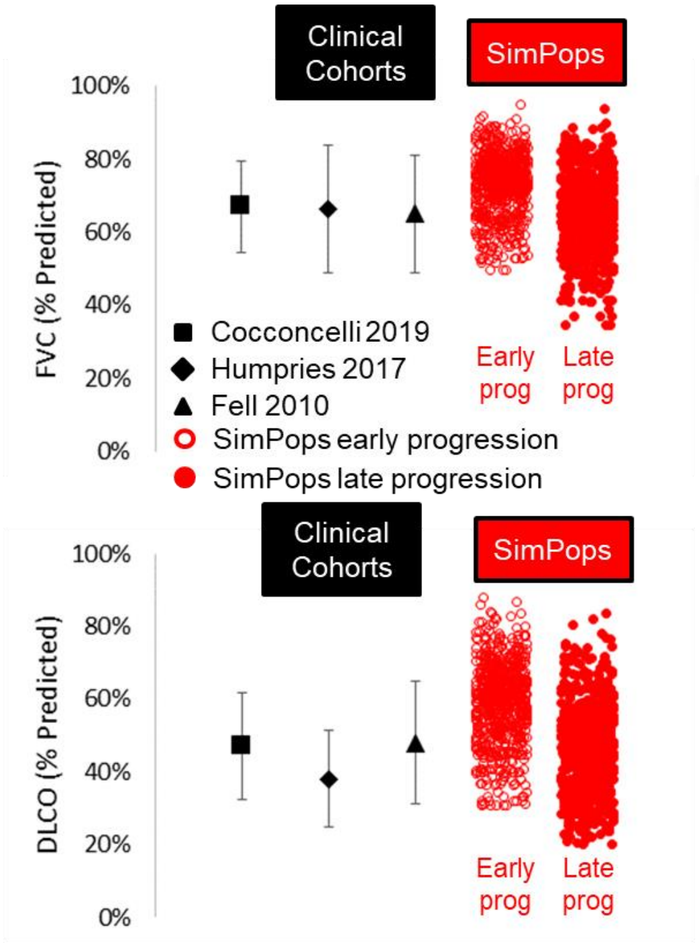
- SimPops patients (n=716) include varying degrees of IPF severity
  - Includes simulated patients early in progression and later in progression
  - All simulated patients survive 4 years of simulated disease progression
- Simulated volume fractions of fibroblastic foci and honeycombing consistent with range of reported clinical data
  - Clinical data collected via HRCT
  - SimPops patients include variability in body and lung size



Park 2016, Balestro 2019

Simulated FVC and D_{LCO} for SimPops Are Consistent with Clinical Data

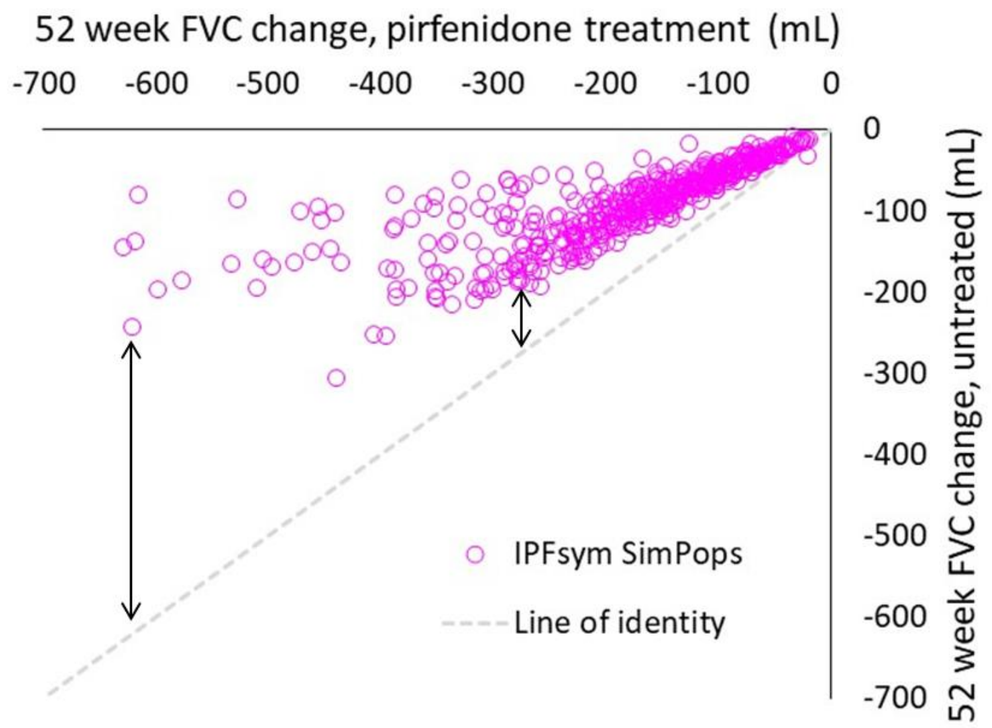
- SimPops patients (n=716) include varying degrees of IPF severity
  - Includes simulated patients early in progression and later in progression
  - All simulated patients survive 4 years of simulated disease progression
- Simulated FVC (% predicted) and D_{LCO} (% predicted) consistent with range of reported clinical data
  - FVC and D_{LCO} measurements compared with reference values for untreated patients of similar age, gender, size
  - Absolute FVC and D_{LCO} are also included as IPFsym clinical outputs
  - FVC and D_{LCO} are influenced by extent of fibroblastic foci and honeycombing within lungs of SimPops patients



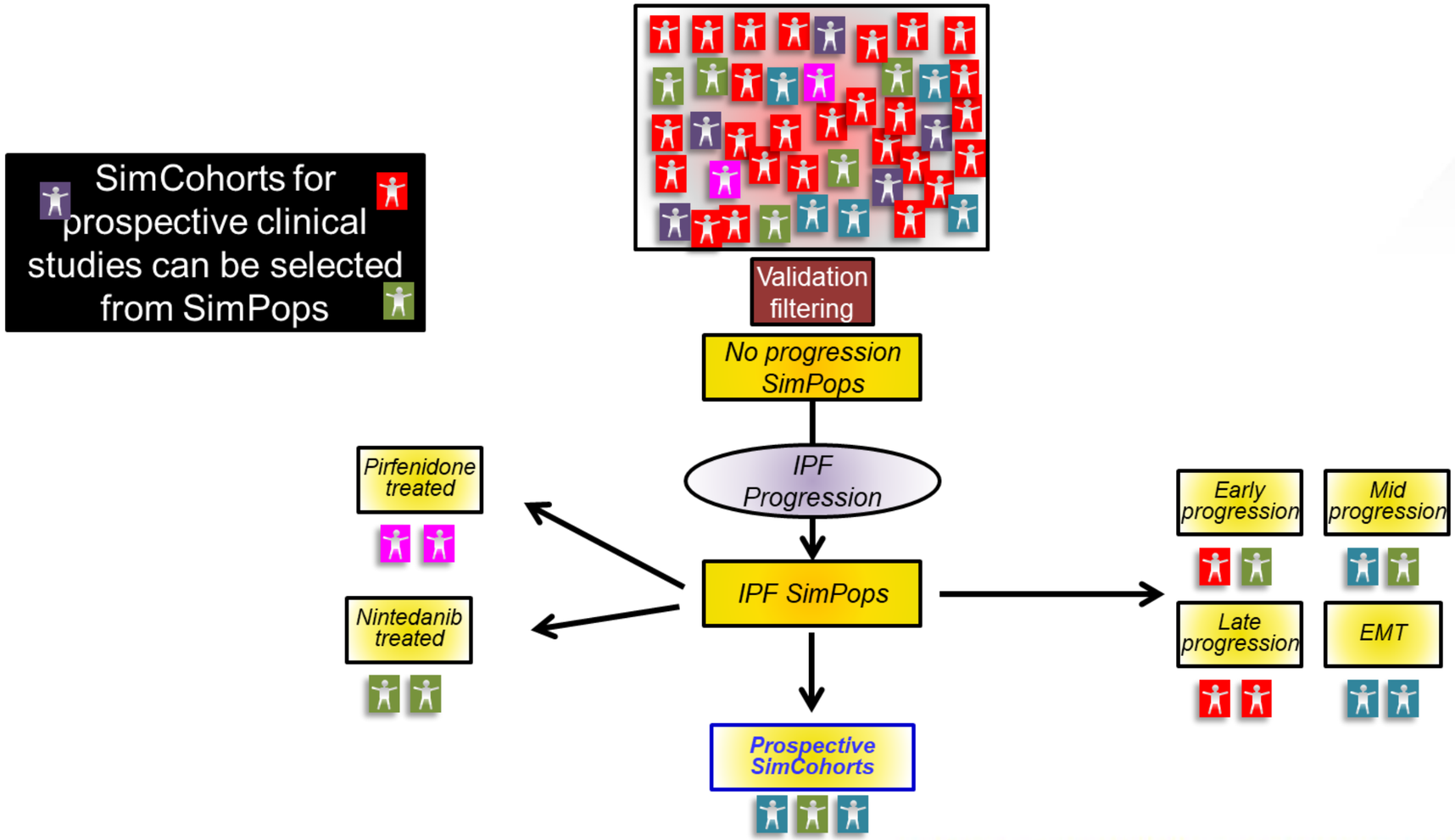
Fell 2010, Humphries 2017, Cocconcelli 2019

Substantial Variability in Predicted Response to Pirfenidone Treatment

- SimPops (n=466) were treated with 801 mg TID pirfenidone for 52 weeks following 52 weeks without treatment
- Pirfenidone treatment predicted to reduce rate of progression
  - FVC change below line of identity
- SimPops patients with greater progression rates predicted to have increased response to pirfenidone
  - Greater distance below line of identity

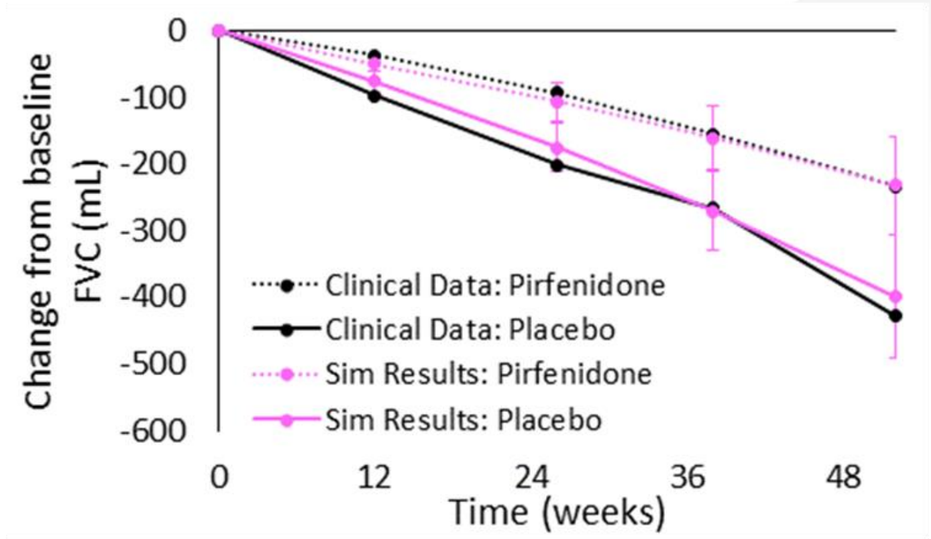


IPFsym v1A SimPops and SimCohorts



Reasonable Simulation of Clinical Response to Pirfenidone Treatment

- SimCohorts (n=62) and clinical IPF patients were treated with 801 mg TID pirfenidone for 52 weeks
  - Similar rate of progression between Clinical IPF patients and SimCohorts patients in placebo group
- Simulated change in FVC on pirfenidone treatment was comparable to clinical data
- Simulated change in FVC with placebo was comparable to clinical data



King 2014

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