Accurate Prediction of Clinical Stroke Scales from Robotic Measurements

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Krebs HI, Krams M, Agrafiotis DK, DiBernardo A, Chavez JC, Littman GS, Yang E, Byttebier G, Dipietro L, Rykman A, McArthur K, Hajjar K, Lees KR, Volpe BT. Robotic measurement of arm movements after stroke establishes biomarkers of motor recovery. *Stroke* **2014**, *45*, 200-204.

Agrafiotis DK, Yang E, Littman GS, Bittebier G, Dipietro L, DiBernardo A, Chavez JC, Rykman A, McArthur K, Hajjar K, Lees KR, Volpe BT, Krams M, Krebs HI. Accurate prediction of clinical stroke scales and improved biomarkers of motor impairment from robotic measurements. *Submitted*.

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Clinical Stroke Scales

- Stroke is one of the leading causes of disability in the US
- Several clinical scales currently in use
  - NIH Stroke Scale (NIH)
  - Fugl Meyer (FM)
  - Motor Power (MP)
  - Modified Rankin (MR)
- Require trained personnel to administer
- Scores vary widely among different raters
- Can only be used for assessment

Advantages of Robotic Devices

- Less sensitive to the skills/expertise of the rater
- Can reduce inter- and intra-rater variability in multi-center trials
- Can reduce sample/effect size required to demonstrate value of therapy
- Can be used simultaneously for both assessment and rehabilitation
- Can be done faster and more frequently
- Could be used in a home setting

Examples of Clinical Stroke Scales

NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)

ITEM	SCORE
Level of consciousness	
Alert	0 points
Drowsy	1 point
Stupor	2 points
Coma	3 points
Response to 2 questions (orientation)	
Know age and current month	0 points
Answers 1 question correctly	1 point
Cannot answer either question correctly	2 points
Response to 2 commands	
Follows 2 commands correctly	0 points
Follows 1 command	1 point
Cannot follow either command	2 points
Best gaze (movement of eyes to left or right)	
Normal eye movements	0 points
Partial gaze paresis to one side	1 point
Forced gaze palsy to one side	2 points
Visual fields	
No visual loss	0 points
Partial homonymous hemianopia	1 point
Complete homonymous hemianopia	2 points
Bilateral visual loss	3 points
Facial motor function	
No facial weakness	0 points
Minor unilateral facial weakness	1 point
Partial unilateral facial weakness	2 points
Complete paralysis of 1 or both sides	3 points
Upper-extremity motor function (right and left scored independently 0 – 8 points)	
Normal movement	0 points
Drift of upper extremity	1 point
Some effort against gravity	2 points
No effort against gravity but moves	3 points
No movement	4 points
Lower-extremity motor function (right and left scored independently 0 – 8 points)	
Normal movement	0 points
Drift of lower extremity	1 point
Some effort against gravity	2 points
No effort against gravity but moves	3 points
No movement	4 points
Limb ataxia (cannot be tested in presence of paresis)	
No limb ataxia	0 points
Ataxia present in 1 limb	1 point
Ataxia present in 2 limbs	2 points
Sensory function	
No sensory loss	0 points
Mild-to-moderate sensory loss	1 point
Severe-to-total sensory loss	2 points
Language	
Normal language	0 points
Mild-to-moderate aphasia	1 point
Severe aphasia	2 points
Mute	3 points
Articulation	
Normal articulation	0 points
Mild-to-moderate dysarthria	1 point
Severe dysarthria	2 points
Extinction or inattention (neglect)	
No neglect or extinction	0 points
Visual or sensory inattention or extinction	1 point
Profound inattention to visual and sensation	2 points

MODIFIED RANKIN SCALE (mRS)

SCORE	IMPAIRMENTS
0	No symptoms at all
1	No disability despite symptoms
2	Slight disability, but does not require assistance
3	Moderate disability, but can walk
4	Moderately severe disability
5	Severe disability, often bedridden
6	Dead

InMotion™ Robotic System

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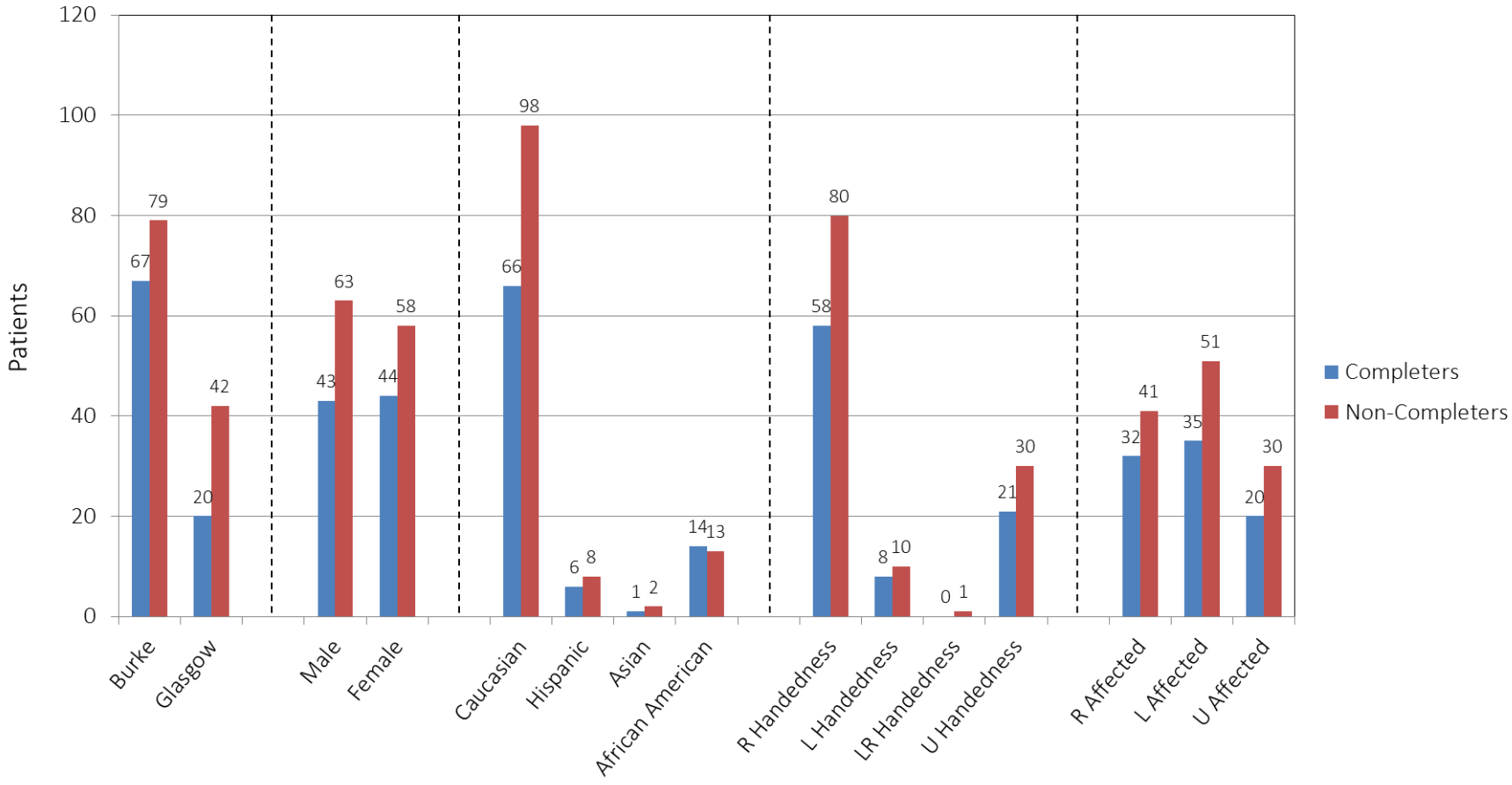
Clinical Study Design

- Objective
  - Design a robotic biomarker with improved effect size over existing clinical scales
- Subjects (n = 208) evaluated at 2 different sites by a singe expert rater at each site
  - Burke (n = 145)
  - Glasgow (n = 63)
- Measurements taken 3, 7, 14, 21, 30 and 90 days post stroke
  - 4 clinical scales (NIH, FM, MR, MP)
  - 35 robotic parameters (RMK)
- Endpoint
  - Improvement of motor function from day 7 to day 90
- Training set (n = 87)
  - Completers (patients with complete measurement profiles for day 7 and day 90)
- Test set (n = 121)
  - Non-completers

Descriptive Statistics



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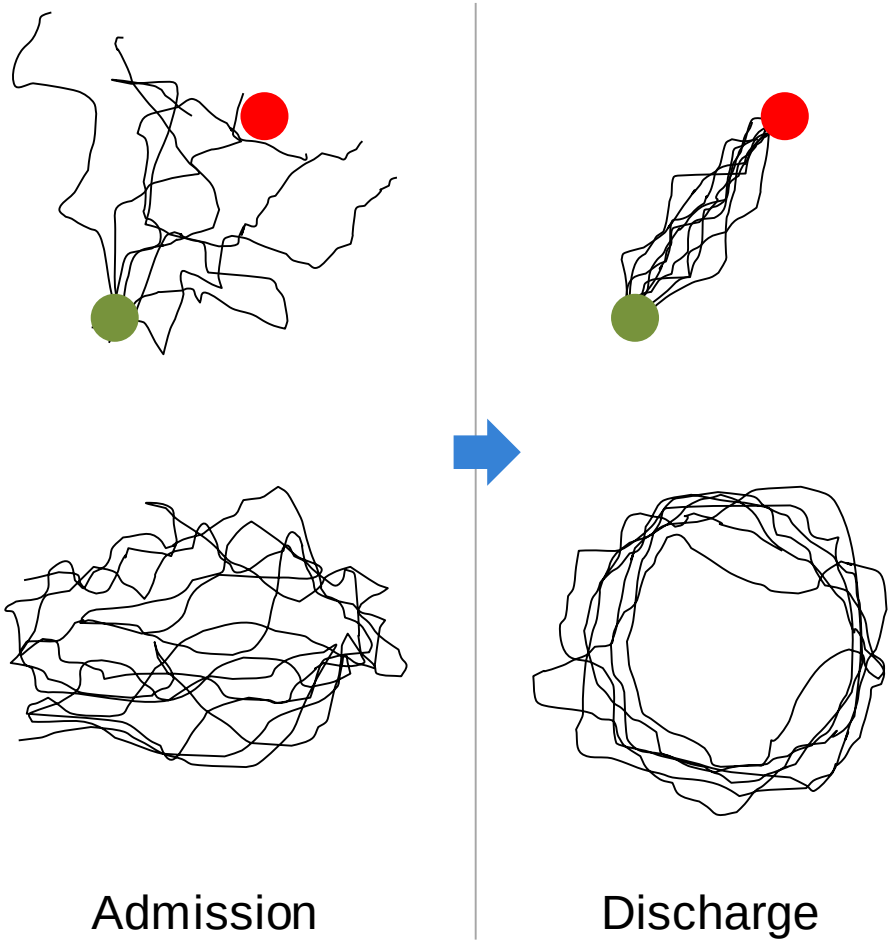
Examples of Robotic Tasks



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Robotically Measured Kinematics (RMK)

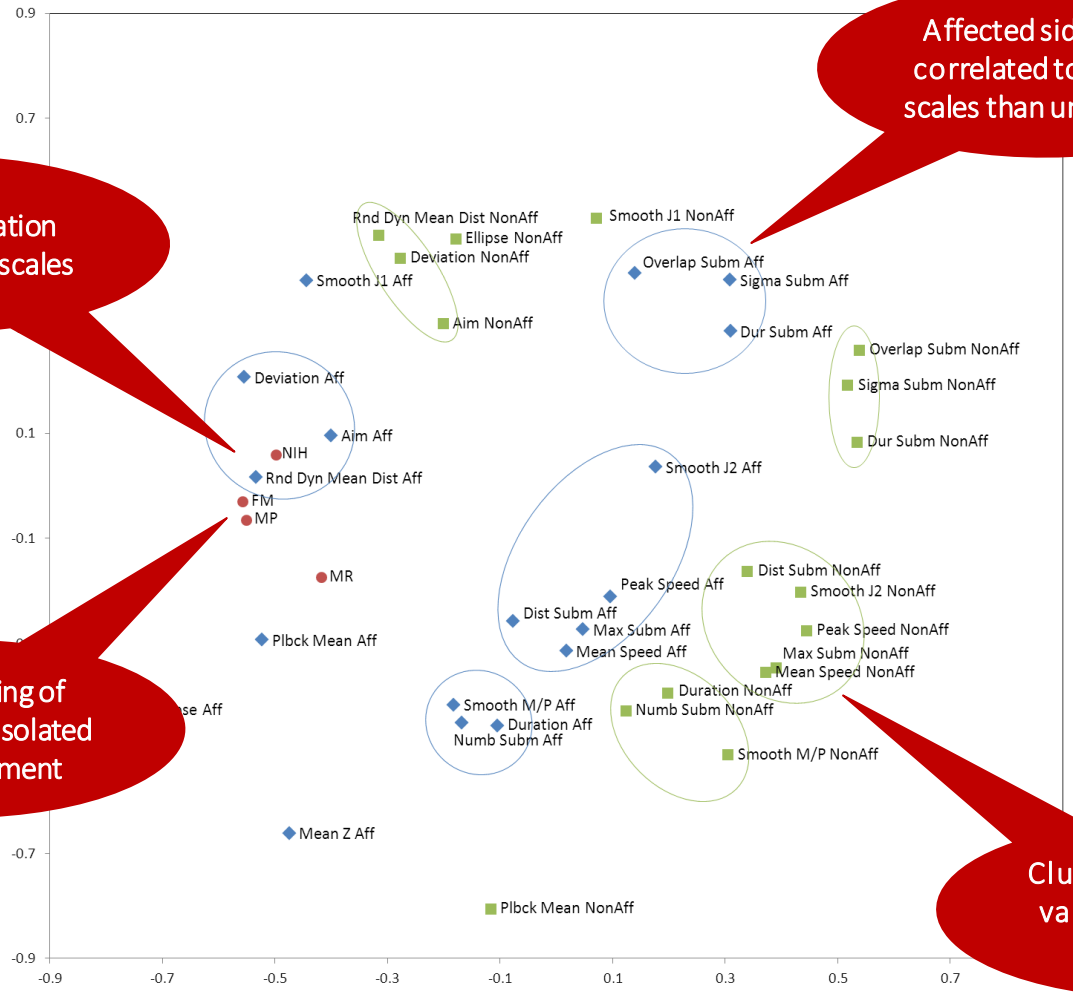
- Reaching (8 marco-metrics and 6 micro-metrics)
  - Deviation from a straight line when reaching for different targets
  - Aim to the targets
  - Average/peak speed and duration of movement
  - Movement mean speed divided by the peak speed
  - Number of peaks in the speed profile
  - Jerk metric which corresponds to the magnitude of jerk divided by the peak speed.
  - Number of sub-movements
  - Duration of sub-movement
  - Degree of sub-movement overlap
  - Sub-movement peak
  - Inter-peak interval
  - Sub-movement skewness/kurtosis
- Circle drawing
  - Ratio of the major to the minor axis of an ellipse fitted to the circle drawing
- Resistance to external forces
  - Ability to move the actuator against a particular level of robotic resistance
  - Ability to keep the robotic actuator still while the robot attempts to move the actuator
- Shoulder strength (affected side only)
  - Mean shoulder strength (Z force) for flexion, extension, abduction and adduction

Data Modeling

$$y = f(x)$$

Patient ID	Day	FM	MP	NIH	MR	Aim NonAff	Aim Aff	Deviation NonAff	Deviation Aff	Mean Speed NonAff	Mean Speed Aff	Peak Speed NonAff	Peak Speed Aff	Smooth M/P NonAff	Smooth M/P Aff	Smooth J1 NonAff	Smooth J1 Aff	Smooth J2 NonAff	Smooth J2 Aff	Duration NonAff	Duration Aff	Ellipse NonAff	Ellipse Aff	Rnd Dyn Mean Dist Non	Rnd Dyn Mean Dist Aff	Plbck Mean NonAff	Plbck Mean Aff	Mean Z Aff	Numb Subm NonAff	Numb Subm Aff	Dur Subm NonAff	Dur Subm Aff	Max Subm NonAff	Max Subm Aff	Sigma Subm NonAff	Sigma Subm Aff	Overlap Subm NonAff	Overlap Subm Aff	Dist Subm NonAff	Dist Subm Aff
80101	3																																						
80101	7	28	35	3		0.22	0.19	0.07	0.07	0.25	0.16	0.28	0.26	0.48	0.42	0.12	0.18	0.05	0.04	0.24	0.43	0.64	1.00	0.83	0.88	0.08	0.17	0.83	0.17	0.35	0.67	0.68	0.22	0.17	0.62	0.58	0.58	0.42	0.43	0.60
80101	14	29	37	3		0.25	0.20	0.11	0.10	0.27	0.15	0.31	0.26	0.49	0.39	0.13	0.18	0.06	0.04	0.23	0.50	0.61	1.00	0.84	0.92	0.16	0.70	0.83	0.18	0.38	0.68	0.73	0.27	0.18	0.60	0.61	0.59	0.53	0.40	0.63
80101	21	34	37	3		0.14	0.11	0.06	0.07	0.31	0.19	0.31	0.24	0.62	0.60	0.15	0.21	0.07	0.05	0.17	0.32	0.75	1.00	0.80	0.87	0.10	0.26	0.83	0.14	0.25	0.64	0.73	0.29	0.18	0.58	0.62	0.60	0.53	0.31	0.55
80101	30	35	38	3	3	0.22	0.12	0.08	0.06	0.33	0.23	0.33	0.28	0.60	0.61	0.15	0.19	0.08	0.06	0.18	0.28	0.65	1.00	0.79	0.87	0.03	0.15	0.83	0.13	0.18	0.66	0.79	0.28	0.22	0.62	0.72	0.67	0.63	0.34	0.61
80101	90																																							
80102	3																																							
80102	7	42	42	8		0.31	0.14	0.16	0.15	0.10	0.30	0.15	0.34	0.27	0.69	0.15	0.20	0.01	0.12	0.54	0.18	0.70	1.00	0.40	0.42	0.08	0.08	0.82	0.45	0.12	0.76	0.63	0.08	0.32	0.64	0.62	0.39	0.54	0.65	0.44
80102	14	47	43	7		0.40	0.22	0.20	0.11	0.15	0.17	0.23	0.29	0.28	0.41	0.09	0.15	0.03	0.04	0.40	0.42	0.73	1.00	0.71	0.56	0.07	0.08	0.82	0.41	0.30	0.66	0.65	0.15	0.21	0.54	0.55	0.41	0.44	0.51	0.55
80102	21	54	54	5		0.27	0.18	0.13	0.07	0.13	0.20	0.17	0.30	0.37	0.48	0.12	0.14	0.02	0.05	0.39	0.33	0.57	1.00	0.81	0.90	0.05	0.03	0.82	0.31	0.23	0.74	0.63	0.14	0.25	0.61	0.53	0.48	0.47	0.50	0.51
80102	30	59	55	5	4	0.30	0.16	0.13	0.06	0.23	0.22	0.29	0.32	0.42	0.51	0.09	0.15	0.05	0.06	0.27	0.28	0.79	1.00	0.83	0.87	0.25	0.48	0.84	0.27	0.24	0.54	0.47	0.21	0.21	0.46	0.40	0.35	0.48	0.40	0.39
80102	90																																							
80103	3																																							
80103	7	4	6	9		0.22	0.25	0.08	0.24	0.31	0.32	0.33	0.35	0.55	0.70	0.13	0.31	0.07	0.17	0.20	0.14	0.86	1.00	0.80	0.18	0.04	0.44	0.82	0.18	0.12	0.59	0.44	0.31	0.33	0.53	0.47	0.50	0.47	0.33	0.31
80103	14	6	17	7		0.24	0.24	0.09	0.24	0.43	0.29	0.48	0.37	0.54	0.64	0.13	0.15	0.11	0.08	0.14	0.24	0.84	1.00	0.80	0.41	0.06	0.36	0.83	0.10	0.18	0.57	0.65	0.46	0.34	0.54	0.62	0.45	0.52	0.28	0.45
80103	21	8	22	7		0.17	0.26	0.04	0.13	0.41	0.19	0.46	0.27	0.54	0.48	0.11	0.21	0.11	0.06	0.11	0.51	0.79	1.00	0.80	0.32	0.03	0.33	0.83	0.08	0.50	0.50	0.49	0.44	0.17	0.45	0.43	0.37	0.37	0.20	0.40
80103	30	9	25	5	4	0.17	0.24	0.05	0.11	0.43	0.18	0.49	0.27	0.52	0.46	0.13	0.22	0.12	0.05	0.10	0.45	0.69	1.00	0.80	0.35	0.02	0.32	0.83	0.06	0.50	0.47	0.44	0.46	0.16	0.46	0.37	0.30	0.33	0.22	0.35
80103	90	10	26	4	3	0.12	0.17	0.04	0.06	0.51	0.23	0.55	0.32	0.57	0.55	0.16	0.14	0.16	0.06	0.07	0.28	0.93	1.00	0.81	0.65	0.06	0.15	0.82	0.02	0.20	0.53	0.62	0.55	0.25	0.54	0.55	0.44	0.48	0.18	0.46
80104	3																																							
80104	7																																							
80104	14	33	36	15		0.51	0.21	0.15	0.16	0.01	0.17	0.07	0.20	0.07	0.58	0.20	0.32	0.00	0.08	0.83	0.29	0.64	1.00	0.58	0.46	0.05	0.04	0.82	0.67	0.23	0.82	0.56	0.04	0.17	0.67	0.51	0.41	0.43	0.71	0.49
80104	21	40	42	12		0.64	0.30	0.25	0.20	0.06	0.16	0.11	0.22	0.25	0.44	0.17	0.32	0.01	0.07	0.60	0.54	0.44	1.00	0.70	0.43	0.06	0.30	0.82	0.51	0.42	0.89	0.67	0.08	0.13	0.73	0.58	0.54	0.43	0.64	0.61
80104	30	49	52	12	4	0.49	0.20	0.24	0.13	0.13	0.19	0.18	0.26	0.34	0.52	0.12	0.21	0.02	0.06	0.44	0.39	0.55	1.00	0.72	0.66	0.34	0.28	0.82	0.33	0.26	0.88	0.79	0.16	0.19	0.77	0.71	0.56	0.56	0.65	0.65
80104	90	52	56	12	4	0.25	0.13	0.05	0.04	0.15	0.16	0.16	0.20	0.46	0.57	0.13	0.23	0.03	0.04	0.31	0.36	0.69	1.00	0.79	0.84	0.11	0.03	0.82	0.21	0.27	0.86	0.74	0.16	0.18	0.76	0.65	0.59	0.57	0.59	0.53
80105	3																																							
80105	7	42	42	7		0.37	0.22	0.13	0.08	0.22	0.29	0.34	0.43	0.30	0.50	0.14	0.12	0.06	0.09	0.28	0.26	0.00	1.00	0.44	0.53	0.25	0.26	0.83	0.35	0.20	0.35	0.56	0.20	0.35	0.30	0.49	0.18	0.41	0.27	0.45
80105	14	54	47	2		0.34	0.17	0.11	0.07	0.34	0.29	0.49	0.40	0.32	0.55	0.09	0.13	0.09	0.09	0.21	0.23	0.19	1.00	0.83	0.87	0.22	0.18	0.83	0.17	0.13	0.45	0.48	0.37	0.36	0.39	0.46	0.26	0.51	0.32	0.39
80105	21	59	47	2		0.29	0.12	0.09	0.04	0.34	0.28	0.48	0.35	0.35	0.64	0.12	0.15	0.09	0.08	0.17	0.20	0.09	1.00	0.83	0.84	0.56	0.12	0.83	0.20	0.16	0.35	0.55	0.35	0.29	0.30	0.49	0.23	0.51	0.22	0.36
80105	30	60	52	2	2	0.20	0.11	0.06	0.05	0.28	0.27	0.32	0.34	0.48	0.64	0.13	0.17	0.06	0.08	0.18	0.21	0.24	1.00	0.83	0.89	0.17	0.03	0.84	0.18	0.17	0.45	0.45	0.27	0.30	0.38	0.42	0.35	0.43	0.22	0.33
80105	90	63	55	1	2	0.26	0.11	0.06	0.05	0.31	0.30	0.38	0.37	0.44	0.65	0.11	0.13	0.08	0.09	0.18	0.18	0.11	1.00	0.80	0.87	0.04	0.36	0.84	0.11	0.13	0.58	0.54	0.32	0.28	0.52	0.53	0.50	0.66	0.34	0.33
80106	3																																							
80106	7	28	27	7		0.16	0.25	0.06	0.24	0.13	0.24	0.13	0.33	0.47	0.61	0.14	0.50	0.02	0.23	0.30	0.24	0.68	1.00	0.78	0.17	0.33	0.41	0.83	0.24	0.32	0.81	0.45	0.10	0.16	0.71	0.40	0.68	0.35	0.48	0.42
80106	14	43	35	3		0.17	0.20	0.10	0.15	0.24	0.27	0.24	0.40	0.58	0.51	0.09	0.18	0.04	0.10	0.22	0.29	0.76	1.00	0.80	0.34	0.27	0.40	0.83	0.13	0.20	0.79	0.66	0.23	0.33	0.71	0.59	0.72	0.44	0.43	0.52
80106	21	44	43	3		0.16	0.24	0.06	0.12	0.19	0.21	0.18	0.39	0.57	0.36	0.11	0.10	0.03	0.06	0.27	0.45	0.86	1.00	0.79	0.83	0.31	0.38	0.84	0.15	0.31	0.87	0.62	0.18	0.29	0.78	0.52	0.70	0.34	0.48	0.63
80106	30																																							
80106	90																																							
80107	3																																							
80107	7	4	4	14		0.13	0.43	0.15	0.19	0.23	0.09	0.17	0.09	0.71	0.67	0.27	0.52	0.08	0.06	0.17	0.17	0.47	1.00	0.30	0.04	0.34	0.45	0.82	0.14	0.10	0.70	0.40	0.18	0.10	0.71	0.42	0.62	0.42	0.34	0.54
80107	14	11	11	11		0.31	0.32	0.27	0.25	0.15	0.10	0.16	0.17	0.45	0.35	0.19	0.26	0.04	0.04	0.35	0.31	0.57	1.00	0.33	0.07	0.44	0.37	0.82	0.36	0.16	0.74	0.64	0.12	0.16	0.63	0.65	0.50	0.51	0.50	0.55
80107	21	20	28	7		0.21	0.12	0.14	0.13	0.18	0.14	0.16	0.17	0.55	0.58	0.29	0.46	0.08	0.12	0.36	0.21	0.74	1.00	0.78	0.20	0.17	0.25	0.82	0.33	0.20	0.73	0.35	0.16	0.12	0.63	0.33	0.49	0.39	0.44	0.35
80107	30	37	43	5	4	0.28	0.12	0.15	0.09	0.20	0.21	0.20	0.27	0.50	0.55	0.28	0.24	0.09	0.08	0.33	0.25	0.74	1.00	0.73	0.43	0.41	0.28	0.82	0.35	0.17	0.61	0.42	0.17	0.24	0.51	0.42	0.37	0.41	0.43	0.35
80107	90																																							

SPE Map of Feature Correlation Matrix



Affected side more correlated to clinical scales than unaffected

Strong correlation among clinical scales

Tight coupling of strength and isolated joint movement

Clusters of correlated variables preserved on both sides

$$d_{ij} = 1 - abs(Rij)$$

Agrafiotis DK, Xu H. *Proc. Natl. Acad. Sci. USA*, **2002**, *99*, 15869-15872
Agrafiotis DK, *J. Comput. Chem.* **2003**, *24*, 1215-1221

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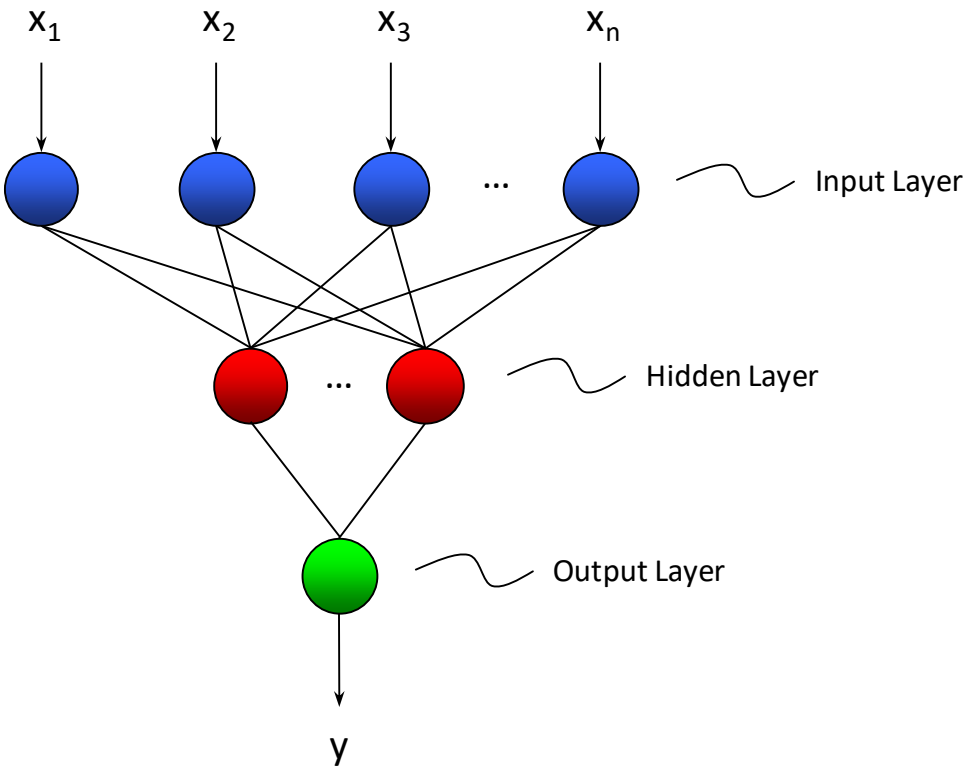
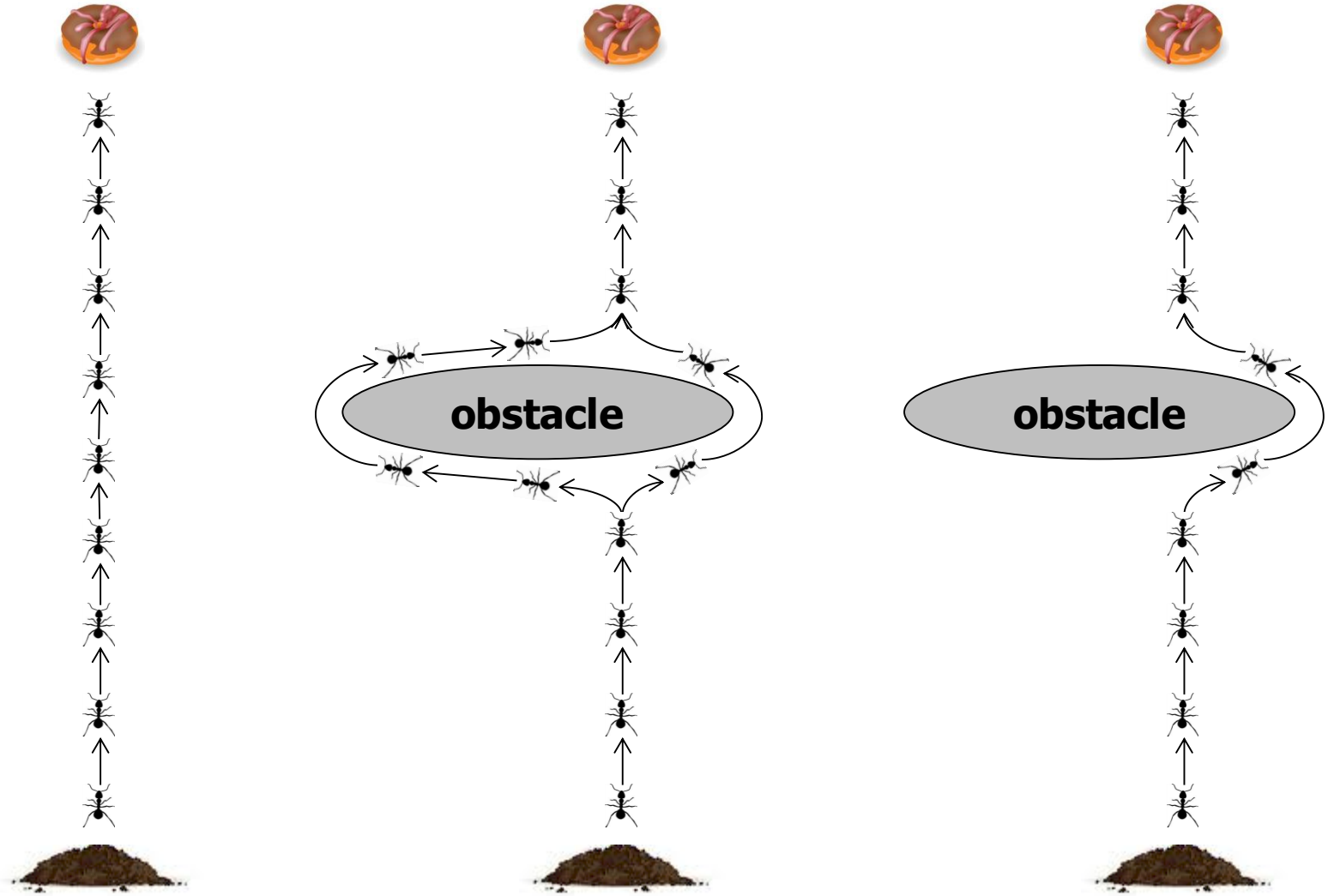
Predicting Clinical Scales

- Learning
- Feature selection
- Cross-validation
- Interpretation

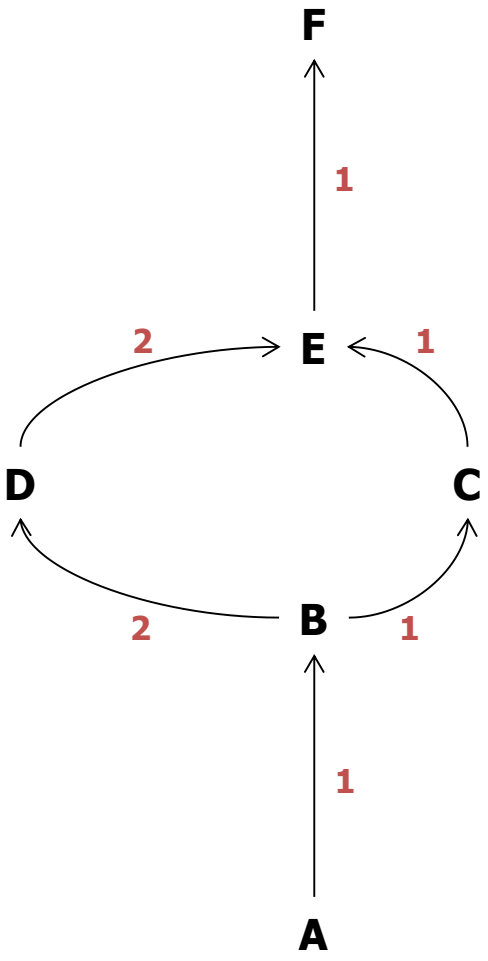
Neural Networks



Ant Colonies



Artificial Ant Colonies



Pheromone intensity on path ij at time t+1

$$\tau_{ij}(t+1) = \rho\tau_{ij}(t) + \Delta\tau_{ij}(t,t+1)$$

ρ – evaporation coefficient

$$\Delta\tau_{ij}(t,t+1) = \frac{Q}{L}$$ – ant-cycle model

Feature Selection Using Artificial Ants

- Choice of the shortest path by the ants

  Choice of the best subset of descriptors

- Length of the path

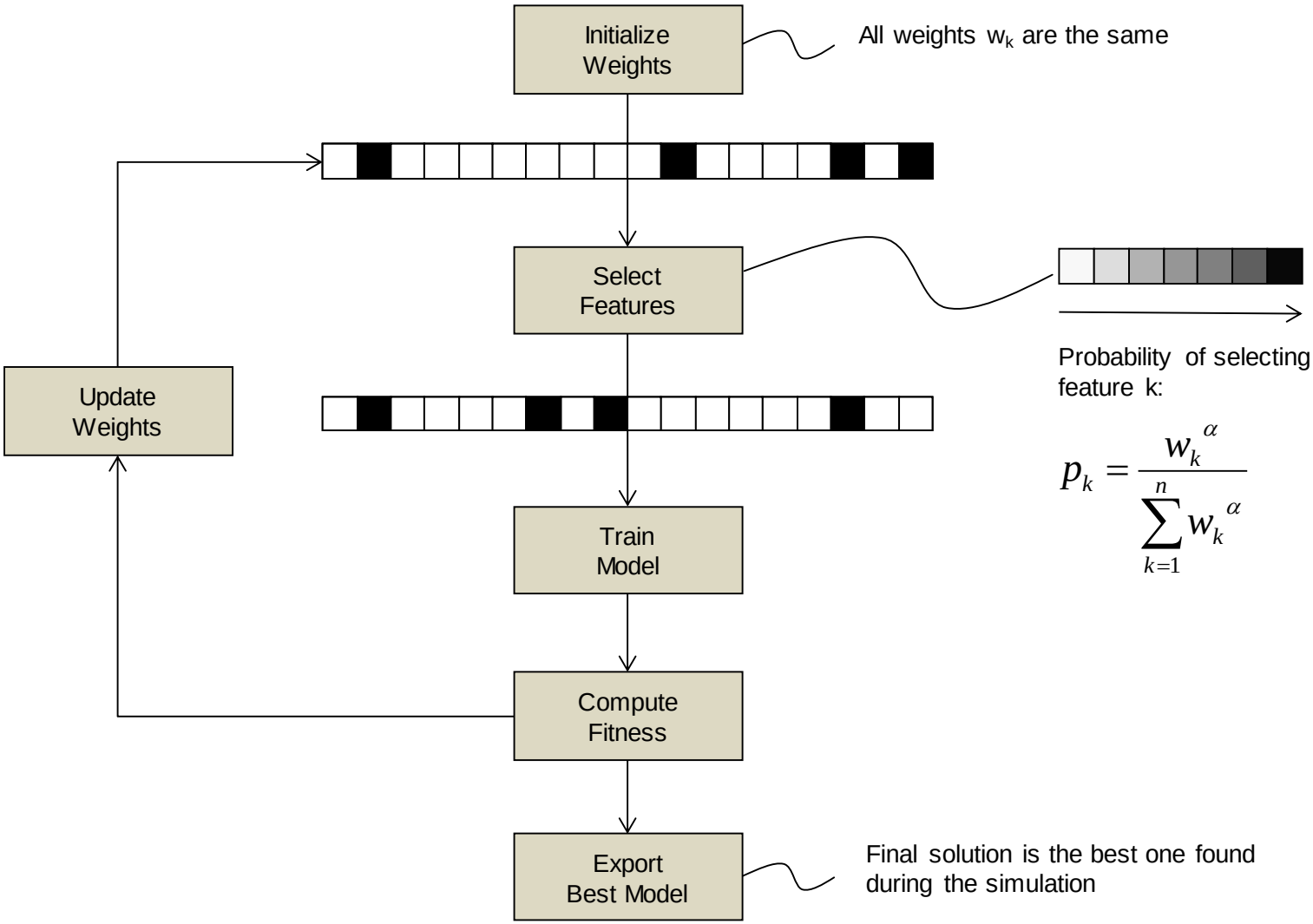
  Fitness of the model based on the subset

- Pheromone deposits

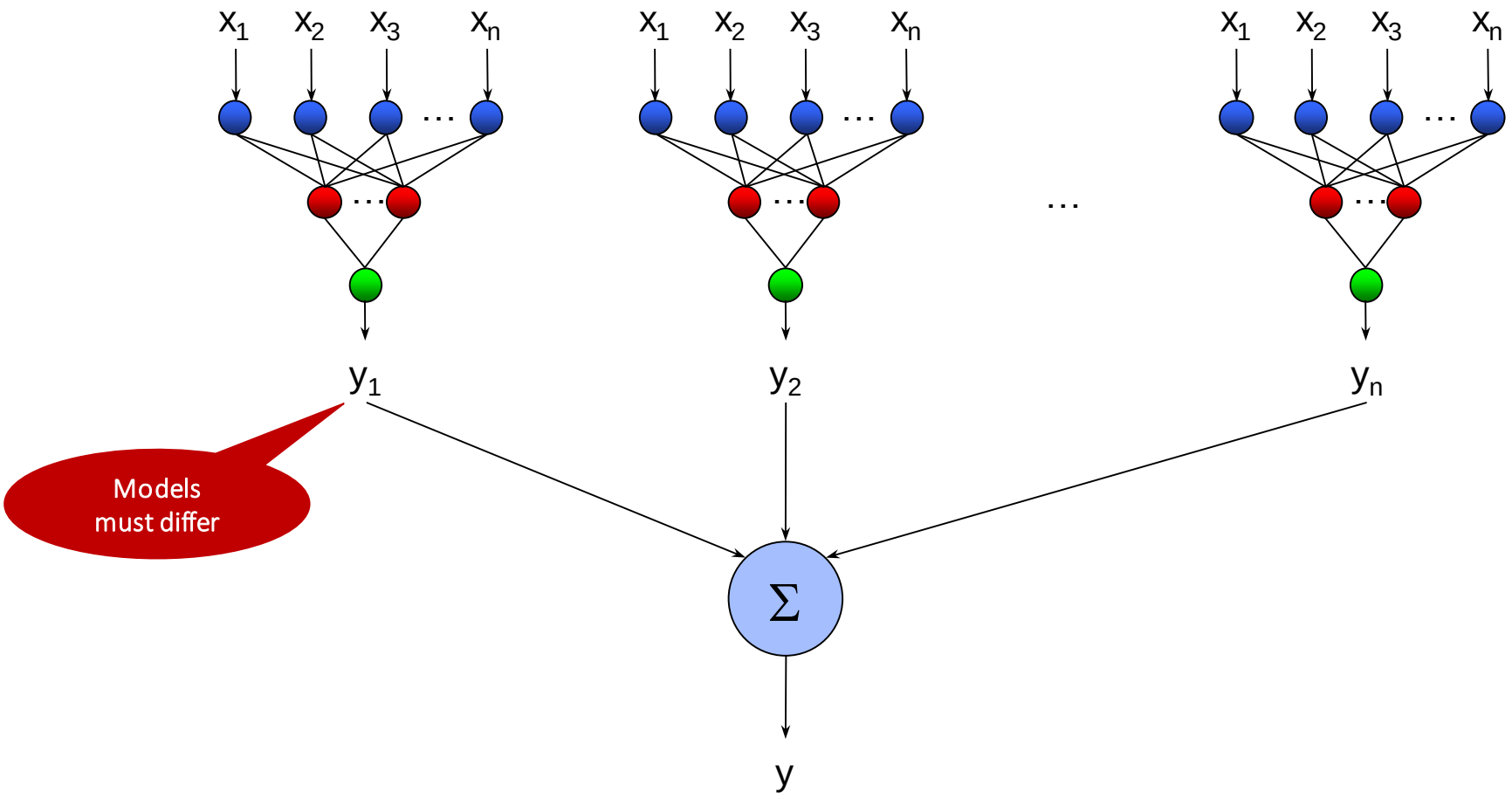
  Probability of including a given descriptor

Izrailev S, Agrafiotis DK. *J. Chem. Inf. Comput. Sci*. **2001**, *41*, 176-180

Feature Selection Using Artificial Ants



Neural Network Ensembles



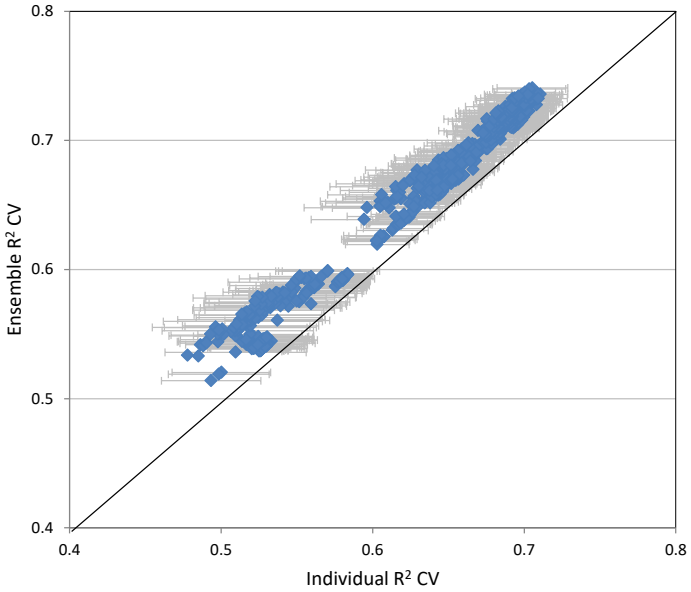
Agrafiotis DK, Cedeño W, Lobanov VS. *J. Chem. Info. Comput. Sci*. **2002**, *42*, 903-911

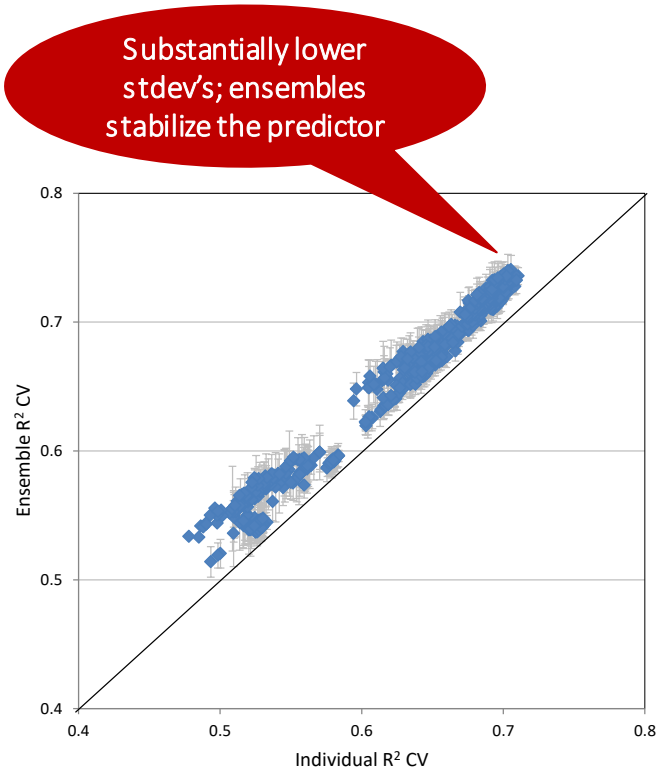
Modeling Protocol

```
for each clinicalScale in {NIH, FM, MR, MP}
{
    for each nFeatures in {2, 4, 6, 8, 10, 12, 14}
    {
        for each nHiddenNeurons in {1, 2, 3}
        {
            for each featureSelectionRun in {1, 2, 3, 4, 5, 6, 7, 8, 9, 10}
            {
                featureSet = SelectFeaturesUsingAntsAndSingleNeuralNet(nFeatures, nHiddenNeurons);
                model = BuildEnsembleModel(featureSet, nHiddenNeurons, nNets = 10);
                r2 = EvaluateModel(model);
                for each crossValidationRun in {1, 2, 3, 4, 5, 6, 7, 8, 9, 10}
                {
                    r2cv = CrossValidateEnsembleModel(model);
                }
                r2test = TestEnsembleModelOnNonCompleters(model);
            }
        }
    }
}
```

// Each reported r2cv is the average over 100 runs (10 x 10)

Individual vs Ensemble CV R2's





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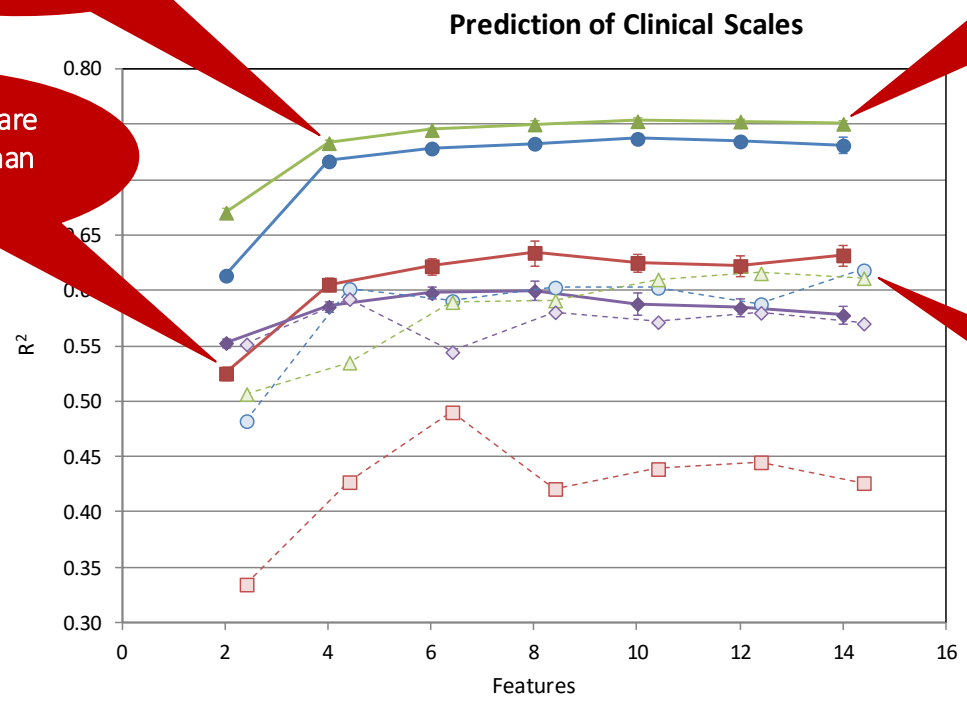
Prediction of Clinical Scales

very good predictions with 4-6 features

FM/MP models are equally predictive

NIH/MR models are less predictive than FM/MP



Models retain predictive power on non-completers

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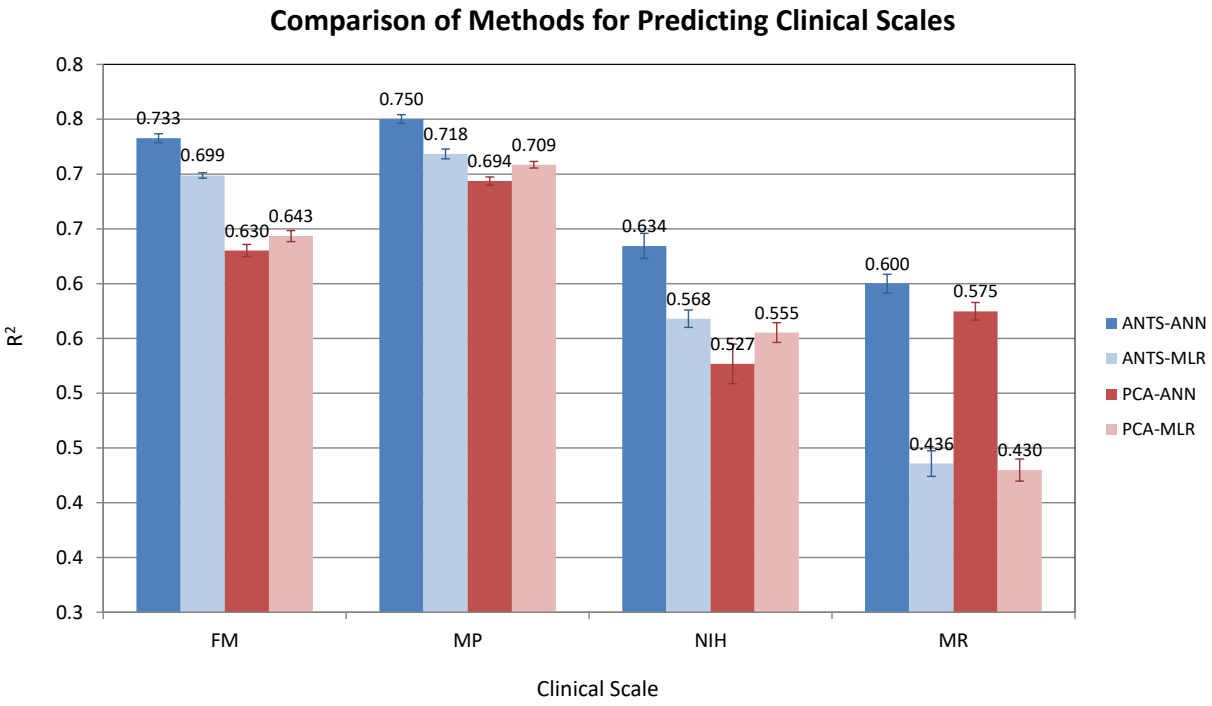
Comparison of Learning Methods



Novel RMK Composites

$$Cohen's\ d = \frac{\mu(s(i,90) - s(i,7))}{\sigma(s(i,90) - s(i,7))}$$

$$c(i) = \sum_{j=1}^{35} w(j) \cdot rmk(i,j)$$

Optimizing Composite Scales

$$
c = \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f1 \quad \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f2 \quad \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f3 \quad \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f4 \quad \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f5 \quad \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f6 \quad \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f7 \quad \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f8
$$

Optimizing Composite Scales

$$c = \quad 0.3 \times f2$$

Optimizing Composite Scales

$$c = 0.3 \times f2 \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f1 \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f3 \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f4 \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f5 \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f6 \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f7 \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f8$$

Optimizing Composite Scales

$$c = \quad 0.3 \times f2 + \text{-}0.7 \times f6$$

Optimizing Composite Scales

$$c = \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f2 + \text{-0.7} \times f6$$

Optimizing Composite Scales

$$c = \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \end{matrix} \; 0.6 \times f2 + \begin{matrix} 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f6$$

Optimizing Composite Scales

$$c = \quad 0.6 \times f2 + \text{-}0.9 \times f6$$

Optimizing Composite Scales

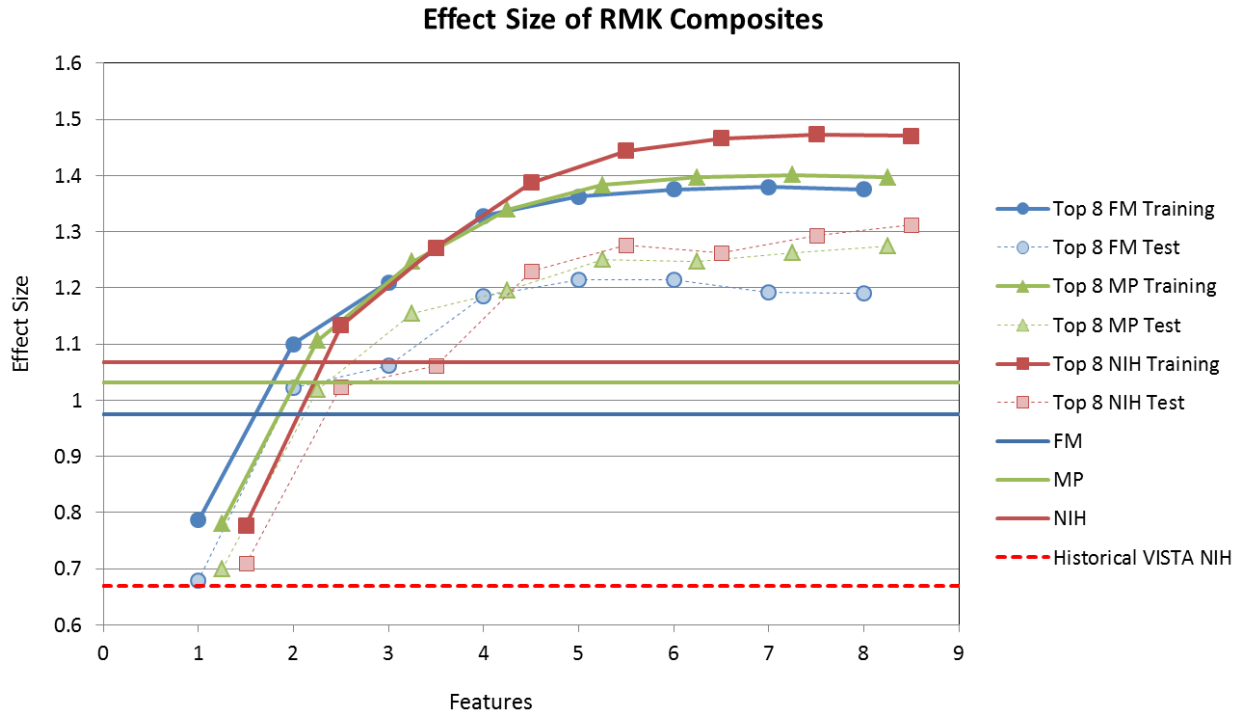
$$c = 0.6 \times f2 + -0.9 \times f6 \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f1 \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f3 \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f4 \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f5 \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f7 \begin{matrix} -1.0 \\ -0.9 \\ -0.8 \\ -0.7 \\ -0.6 \\ -0.5 \\ -0.4 \\ -0.3 \\ -0.2 \\ -0.1 \\ 0.0 \\ 0.1 \\ 0.2 \\ 0.3 \\ 0.4 \\ 0.5 \\ 0.6 \\ 0.7 \\ 0.8 \\ 0.9 \\ 1.0 \end{matrix} \times f8$$

Optimizing Composite Scales

$$c = 0.5 \times f2 + -0.6 \times f6 + 0.3 \times f8 + 0.8 \times f7 + -1.0 \times f5 + -0.8 \times f4 + 0.3 \times f1 + 0.9 \times f3$$

Novel RMK Composites

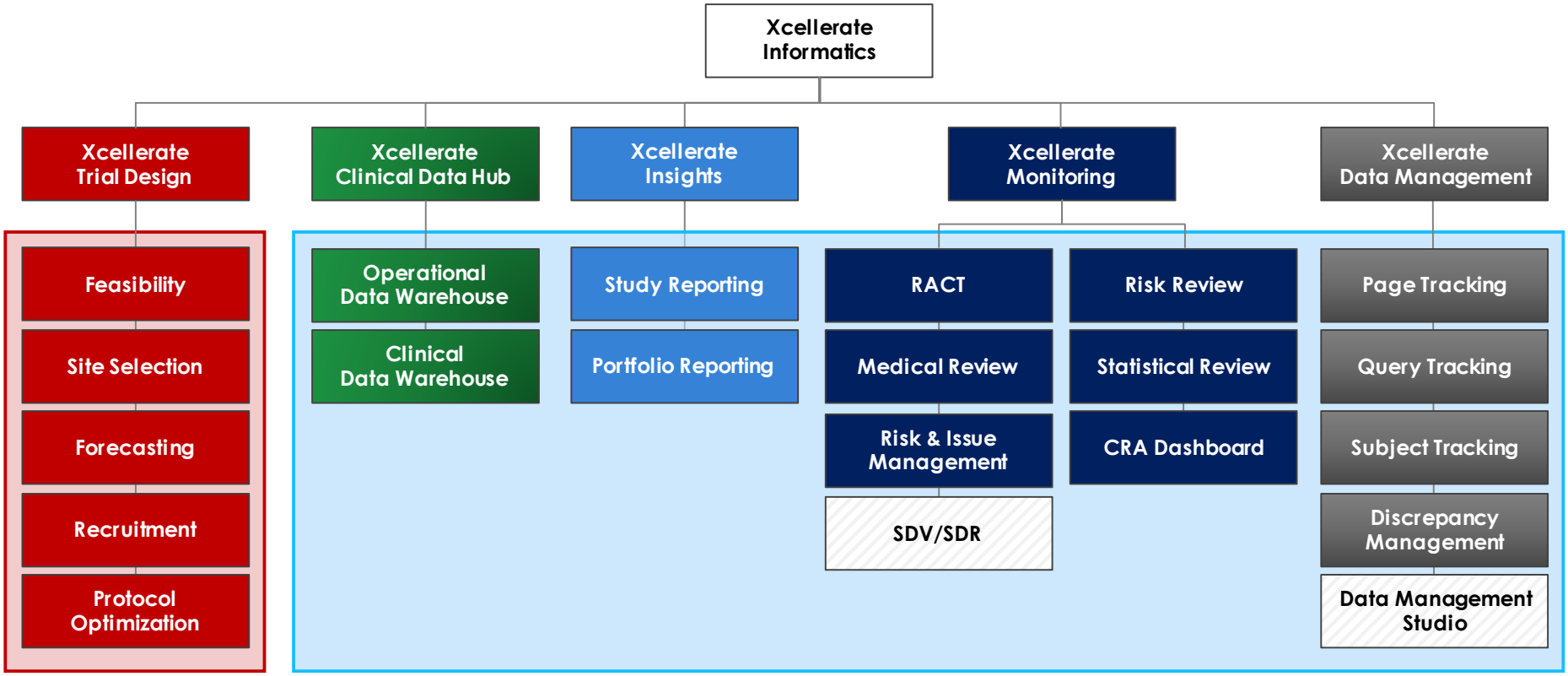
$$Cohen's\ d = \frac{\mu(s(i,90) - s(i,7))}{\sigma(s(i,90) - s(i,7))}$$



$$c(i) = \sum_{j=1}^{35} w(j) \cdot rmk(i,j)$$

Fast Forward to Xcellerate®

Xcellerate Suite



Full Service

Designed for internal use in full-service trials. Powered by proprietary data.

SaaS or Full Service

Designed as a standalone SaaS solution and also used in full-service trials.
Powered by proprietary algorithms (not data).
Modular, agnostic solution, available out-of-the-box

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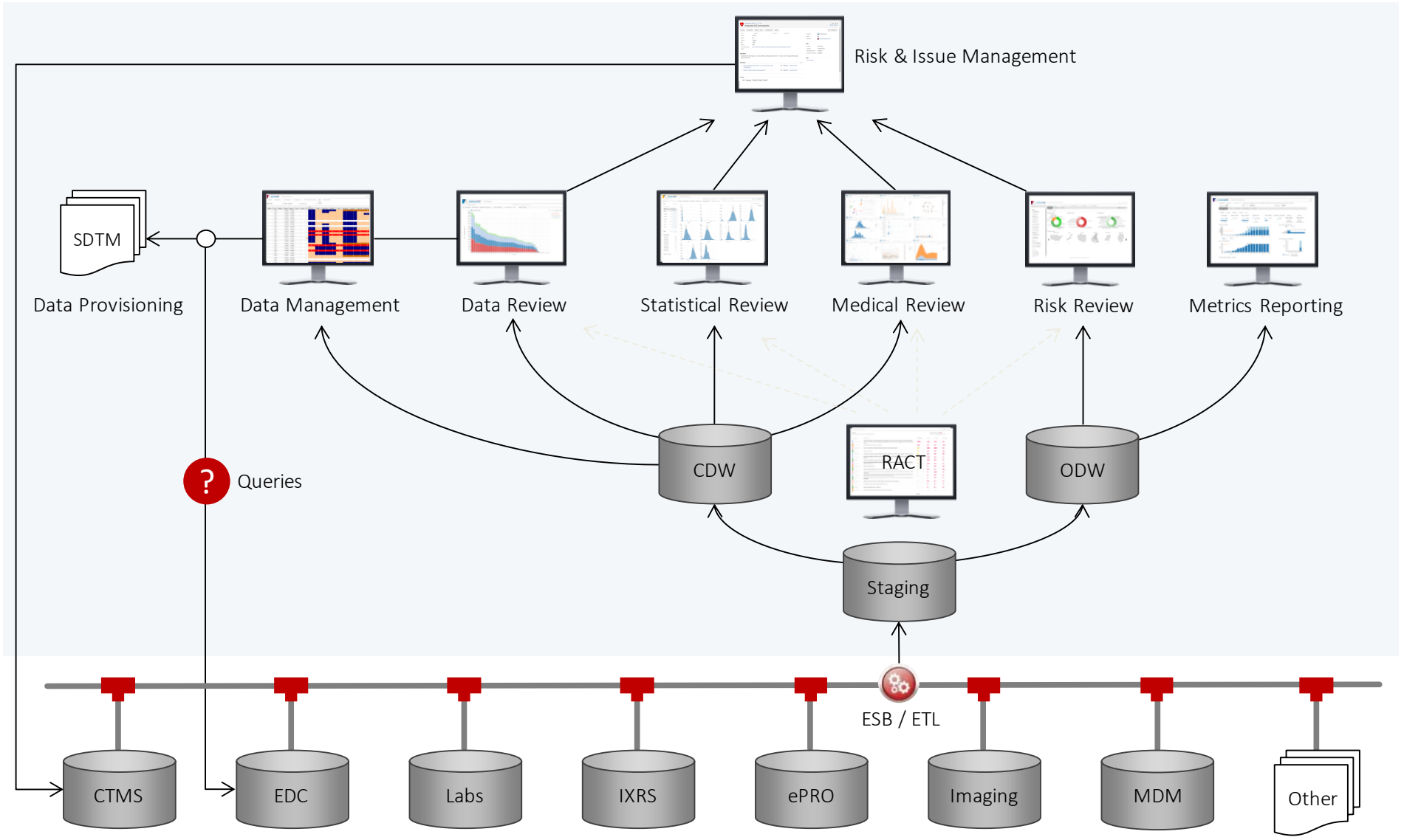
Modular, System-Agnostic Architecture



Clinical Data Warehouse (CDW)

- State-of-the-art data warehouse for preclinical and clinical development
- Modern NoSQL technology that stores data as JSON documents
- Integrates data from multiple sources (EDC, labs, biomarkers, imaging, ePRO…)
- Refreshed daily, suitable for both ongoing and historical studies
- Highly extensible, easy to add new data types (endpoints, labs, biomarkers, etc.)
- Dynamic mapping upon data request (ELT), obviating the need to persist data cuts
- Transformation to multiple output formats without additional storage
- Ability to apply historical maps to current data and current maps to historical data
- Extremely fast and highly scalable data loading and querying
- Full audit trail, no data overrides
- Bidirectional replication, robust failover for both loading and querying
- Robust foundation for real-time monitoring of clinical trials
- Ideal framework for cross-trial analysis and translational research

CDW Data Mapping and Standardization

CSV file from lab vendor

```
subject,site,visit,testcd,value,dat
0001,1,1,AST,5,2017-10-07
0001,1,1,ALT,6,2017-10-07
```

ODM file from EDC

```
<?xml version="1.0" encoding="UTF-8"?>
<ODM xmlns="http://www.cdisc.org/ns/odm/v1.3">
    <ClinicalData StudyOID="MyStudy" MetaDataVersionOID="1">
        <SubjectData SubjectKey="1" TransactionType="Upsert">
            <SiteRef LocationOID="1"/>
            <StudyEventData StudyEventOID="V1">
                <FormData FormOID="DM">
                    <ItemGroupData ItemGroupOID="DM">
                        <ItemData ItemOID="SEX" Value="M"></ItemData>
                        <ItemData ItemOID="AGE" Value="31"></ItemData>
                    </ItemGroupData>
                </FormData>
                <FormData FormOID="SV">
                    <ItemGroupData ItemGroupOID="SV">
                        <ItemData ItemOID="VISITDATE" Value="2017-10-05">
                        </ItemData>
                    </ItemGroupData>
                </FormData>
            </StudyEventData>
        </SubjectData>
    </ClinicalData>
</ODM>
```

Source Record Assembly

```
{
    "domain": "LB",
    "data": {
        "subject": "0001",
        "site": "1",
        "visit": "1",
        "testcd": "AST",
        "value": "5",
        "dat": "10/07/2017"
    }
}
{
    "domain": "LB",
    "data": {
        "subject": "0001",
        "site": "1",
        "visit": "1",
        "testcd": "ALT",
        "value": "6",
        "dat": "10/07/2017"
    }
}
{
    "domain": "DM",
    "data": {
        "StudyOID": "MyStudy",
        "MetaDataVersionOID": "1",
        "SubjectKey": "1",
        "LocationOID": "1",
        "StudyEventOID": "V1",
        "FormOID": "DM",
        "ItemGroupOID": "DM",
        "SEX": "M",
        "AGE": "31"
    }
}
{
    "domain": "SV",
    "data": {
        "StudyOID": "MyStudy",
        "MetaDataVersionOID": "1",
        "SubjectKey": "1",
        "LocationOID": "1",
        "StudyEventOID": "V1",
        "FormOID": "SV",
        "ItemGroupOID": "SV",
        "VISITDATE": "2017-10-05"
    }
}
```

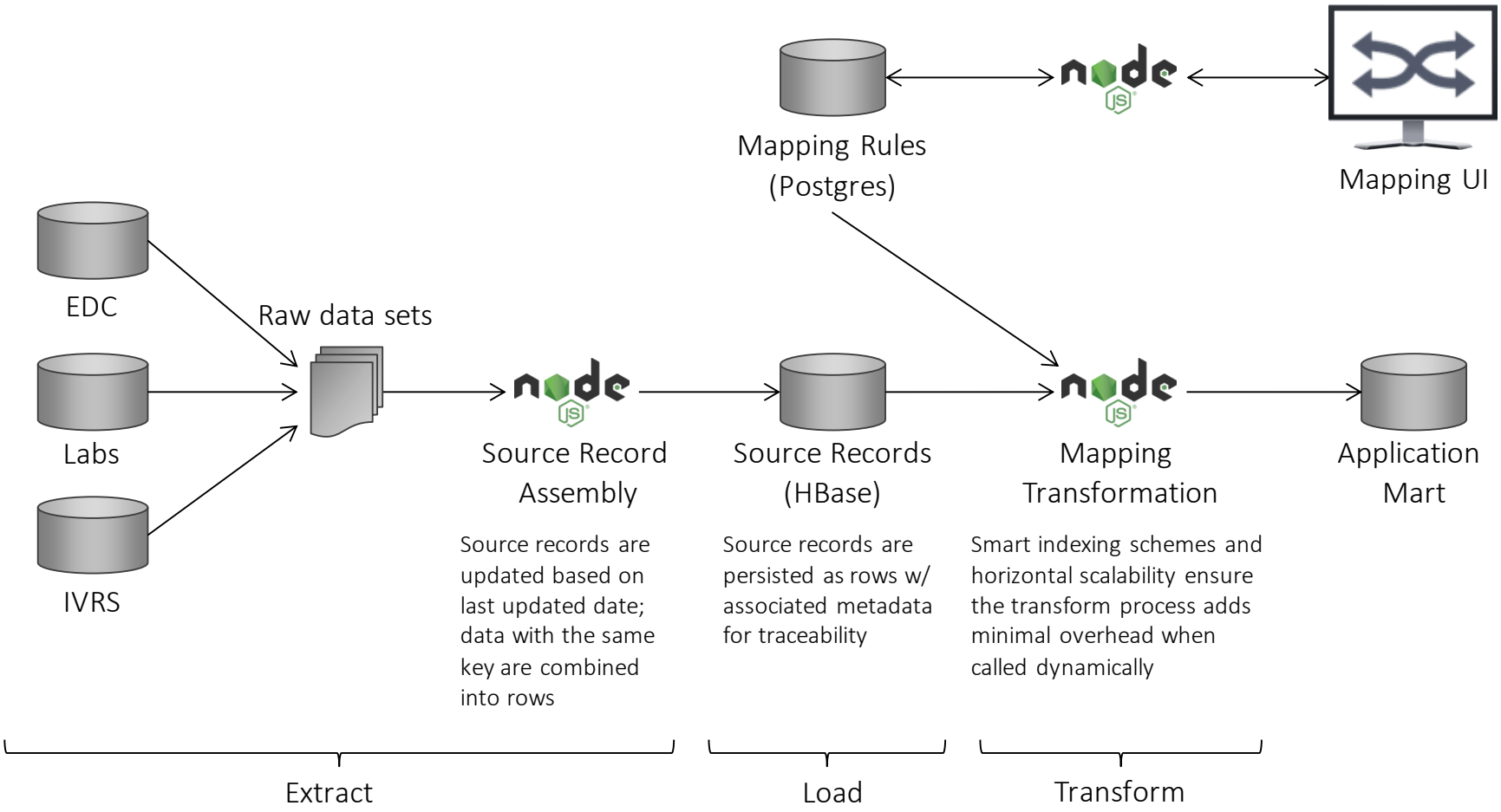
Mapping

```
{
    "STUDYID": "MyStudy",
    "DOMAIN": "LB",
    "SUBJID": "1",
    "SITEID": "1",
    "VISITNUM": "1",
    "TESTCD": "AST",
    "ORRES": "5",
    "DTC": "2017-10-07",
    "DY": "3"
}
{
    "STUDYID": "MyStudy",
    "DOMAIN": "LB",
    "SUBJID": "1",
    "SITEID": "1",
    "VISITNUM": "1",
    "TESTCD": "ALT",
    "ORRES": "6",
    "DTC": "2017-10-07",
    "DY": "3"
}
{
    "STUDYID": "MyStudy",
    "DOMAIN": "DM",
    "SUBJID": "1",
    "SITEID": "1",
    "VISITNUM": "1",
    "SEX": "Male",
    "AGE": "31",
    "RFSTDTC": "2017-10-05"
}
{
    "STUDYID": "MyStudy",
    "DOMAIN": "SV",
    "SUBJID": "1",
    "SITEID": "1",
    "VISITNUM": "1",
    "DTC": "2017-10-05"
}
```

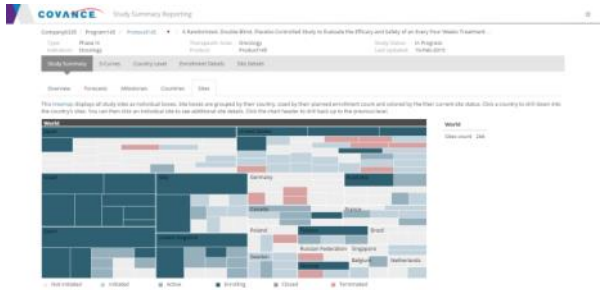
CDW Mapping Transformations

- Column renaming transformations
  - Ensure that identical concepts are identified the same way (Gender vs Sex)
- Code list transformations
  - Ensure identical representation of the same concepts
  - (M,F) → (Male, Female)
  - (0, 1) → (Male, Female)
- Functional transformations
  - Unit transformations, date conversions, basic row-level calculations
- Join transformations
  - Allow data from different sources to be combined into a single row
- Pivot/depivot transformations
  - Convert from one to multiple observations per row and vice versa
  - Some apps may want data pivoted, others depivoted

CDW Architecture



Study Metrics



Benefits

- Near real time access to a wide range of metrics and KPIs to track the progress of the study
- Configurable and extensible metrics and KPIs
- Interactive visualizations with dynamic filtering capabilities
- Drill-down to individual site information and detail-on-demand
- Fully automated data ingestion and mapping process, with no human intervention from acquisition to presentation
- The truth, the whole truth, and nothing but the truth

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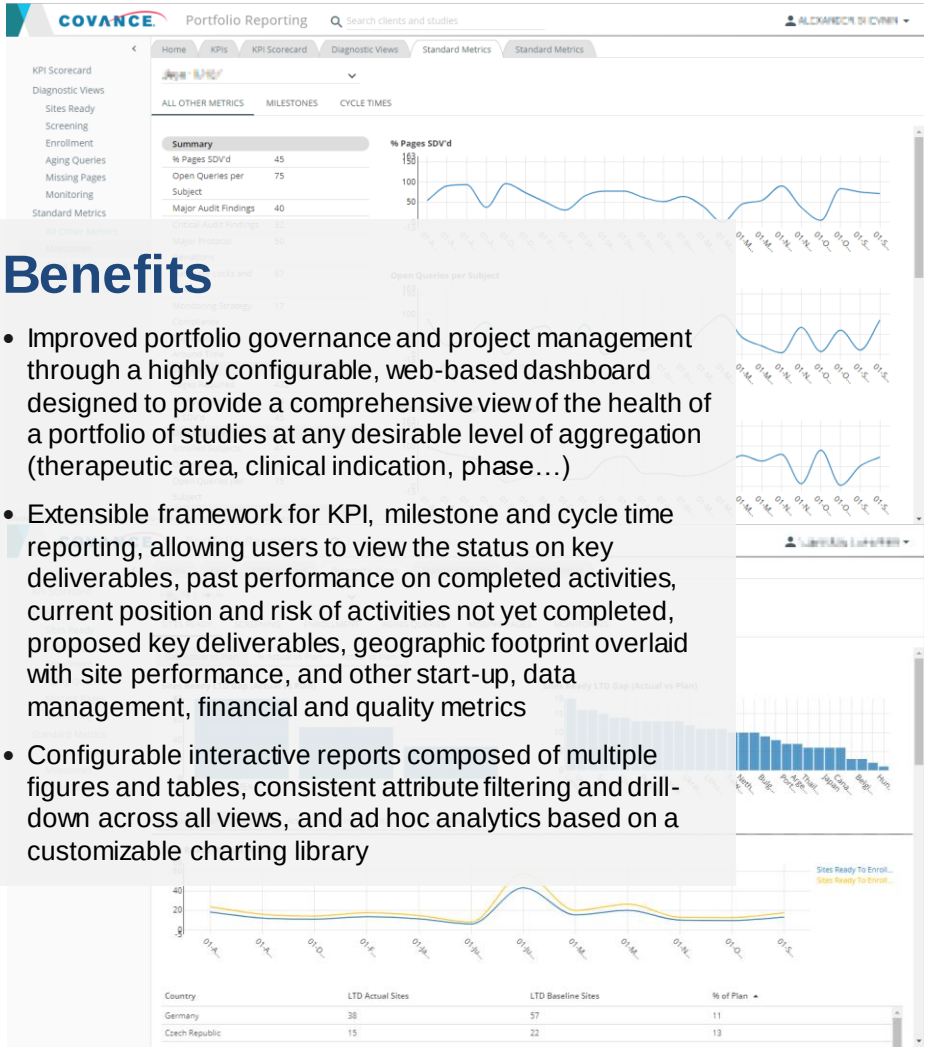
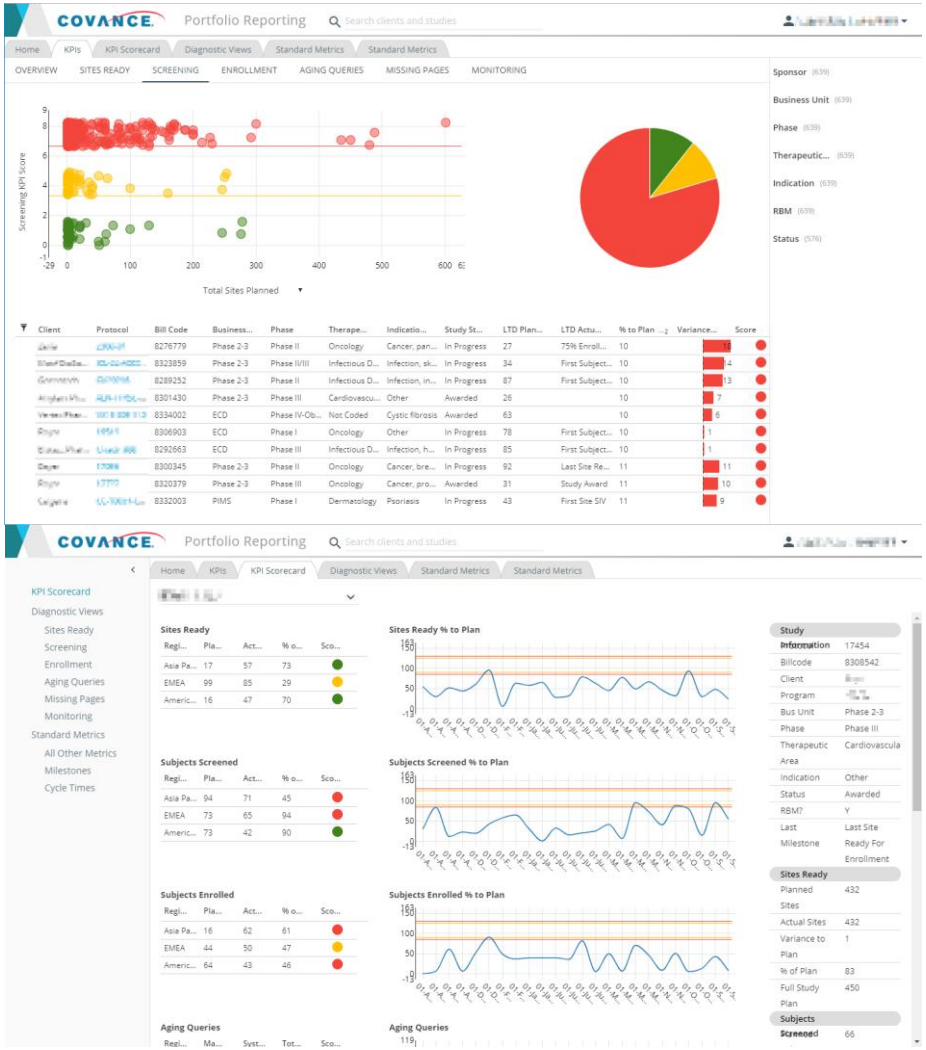
Portfolio Metrics





Benefits

- Improved portfolio governance and project management through a highly configurable, web-based dashboard designed to provide a comprehensive view of the health of a portfolio of studies at any desirable level of aggregation (therapeutic area, clinical indication, phase…)
- Extensible framework for KPI, milestone and cycle time reporting, allowing users to view the status on key deliverables, past performance on completed activities, current position and risk of activities not yet completed, proposed key deliverables, geographic footprint overlaid with site performance, and other start-up, data management, financial and quality metrics
- Configurable interactive reports composed of multiple figures and tables, consistent attribute filtering and drill-down across all views, and ad hoc analytics based on a customizable charting library

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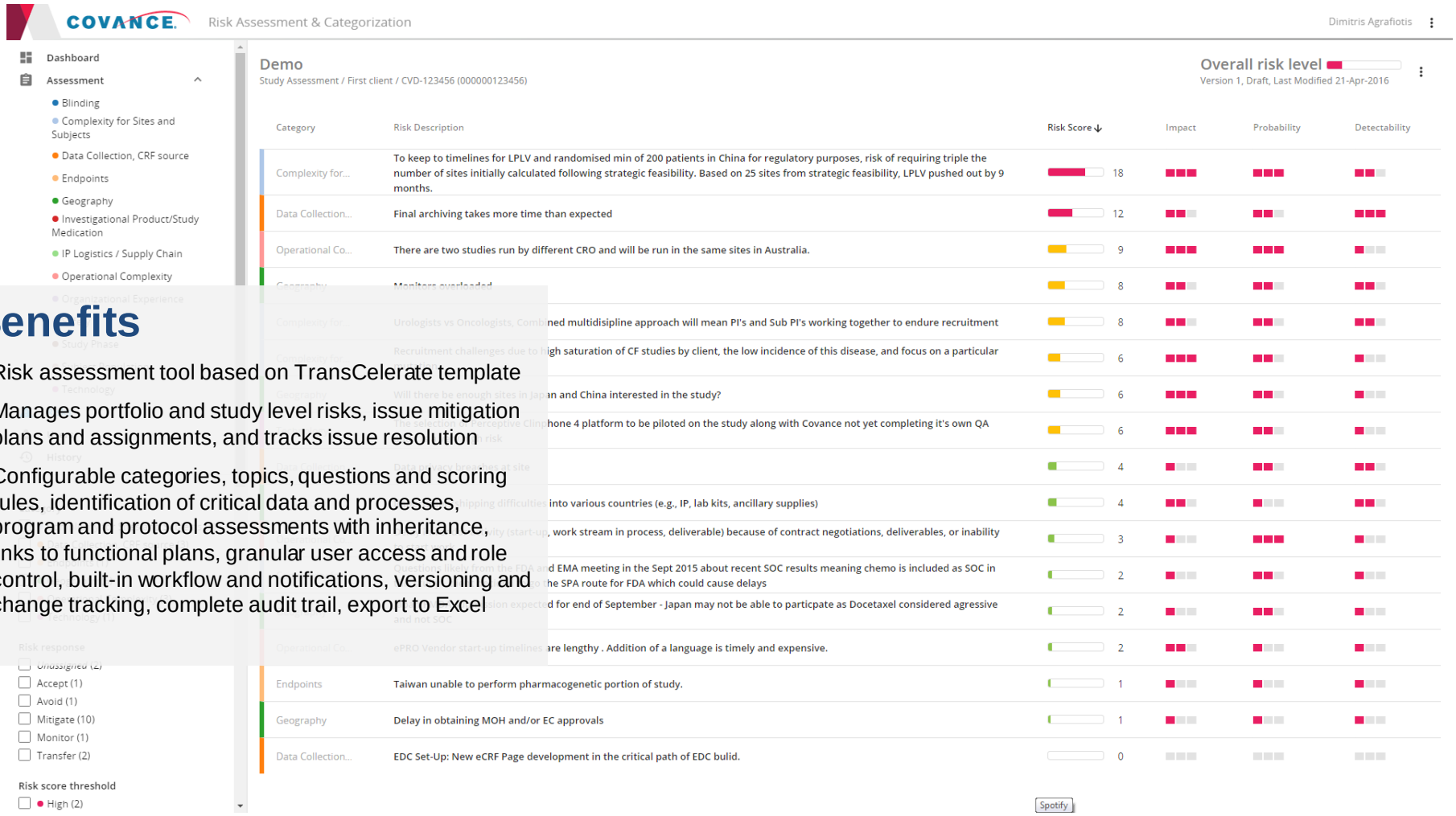
Risk Assessment / RACT



Benefits

- Risk assessment tool based on TransCelerate template
- Manages portfolio and study level risks, issue mitigation plans and assignments, and tracks issue resolution
- Configurable categories, topics, questions and scoring rules, identification of critical data and processes, program and protocol assessments with inheritance, links to functional plans, granular user access and role control, built-in workflow and notifications, versioning and change tracking, complete audit trail, export to Excel

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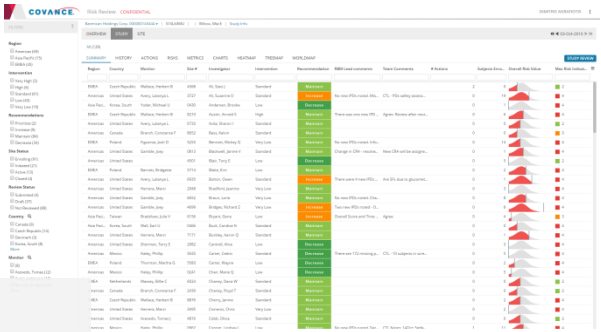
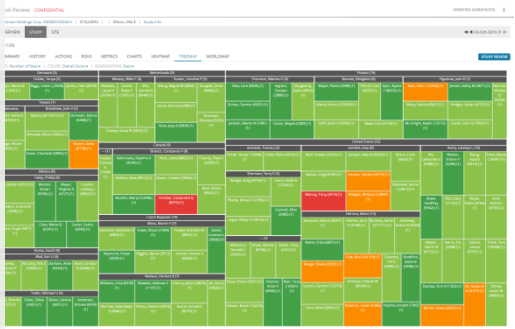
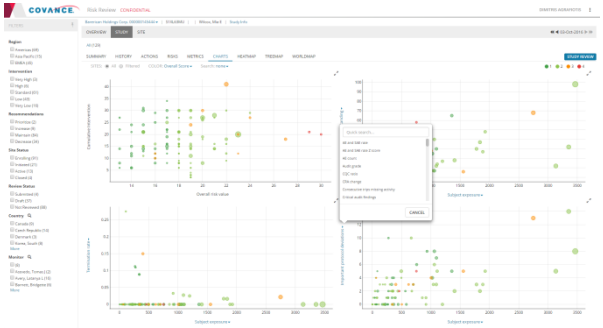
Risk Review

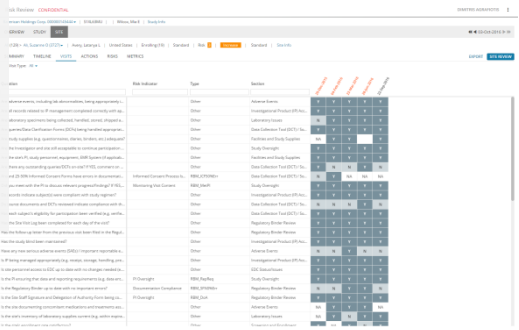


Benefits

- Holistic assessment and mitigation of risk at the study, site and patient level
- Adaptive / tailored intervention depending on site risk
- Improved study risk management via triggered site interventions
- Comprehensive issue management with auditable record of mitigations
- Early detection of problems, proactive risk management
- Improve quality through intelligent spending of monitoring budget
- Full transparency and oversight of CRO conduct and performance
- Full state of control provable to the regulatory agencies







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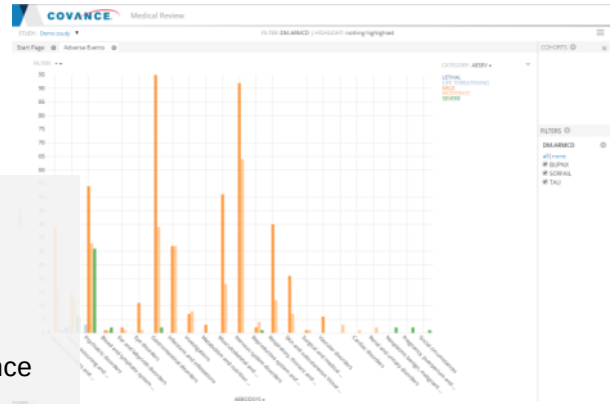
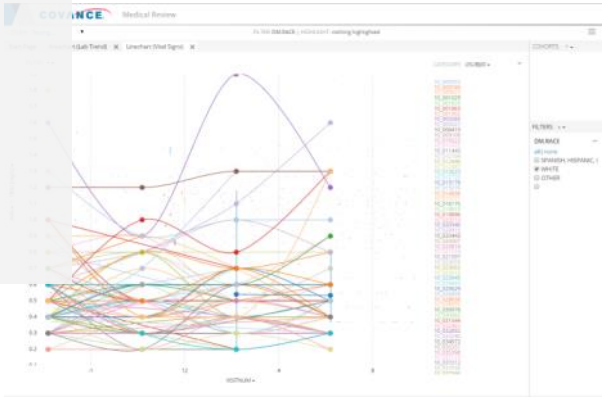
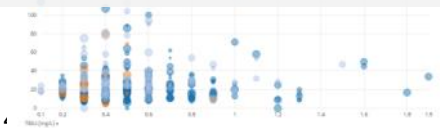
Medical Review



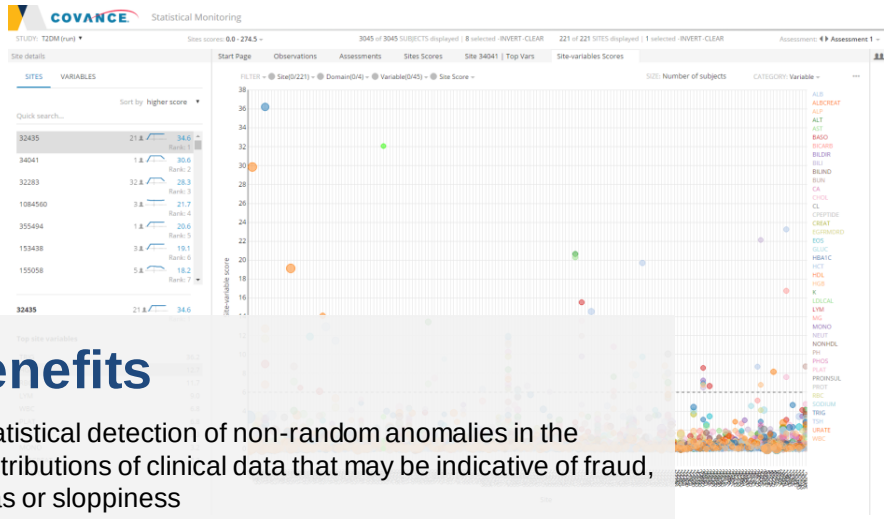


Benefits

- Integrated access to all clinical data from virtually any source with native support for SDTM
- Intuitive data visualizations enabling findings at a glance
- Ability to focus on subgroups of importance or outliers
- Ability to create, highlight and compare arbitrary cohorts
- One-click drill-down to patient and site-level data
- Longitudinal views, patient profiles
- Automatic alerts and notifications according to specified triggers
- Configurable workflows to enable efficient and effective clinical and safety review
- Ability to create, manage and communicate auditable observations
- Better adherence to protocol requirements for subject enrollment
- Avoidance of unnecessary discontinuations
- Reduction in protocol deviations
- Earlier detection of data quality issues

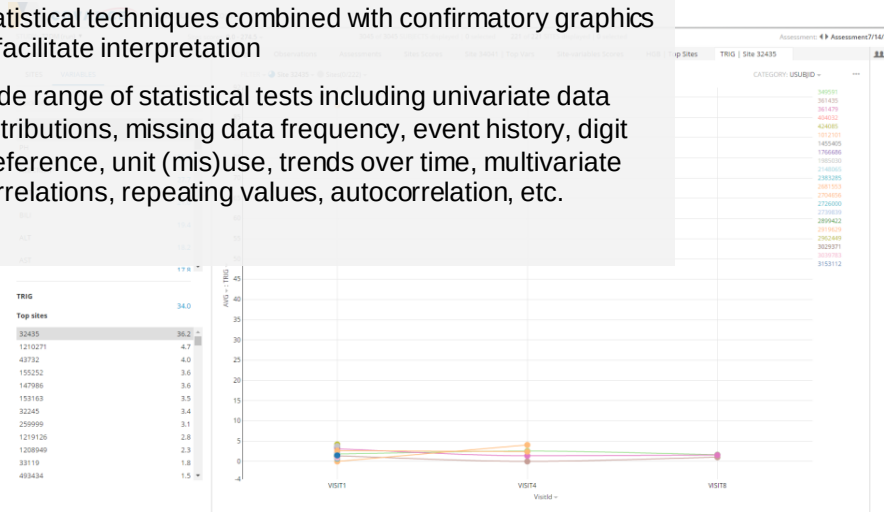


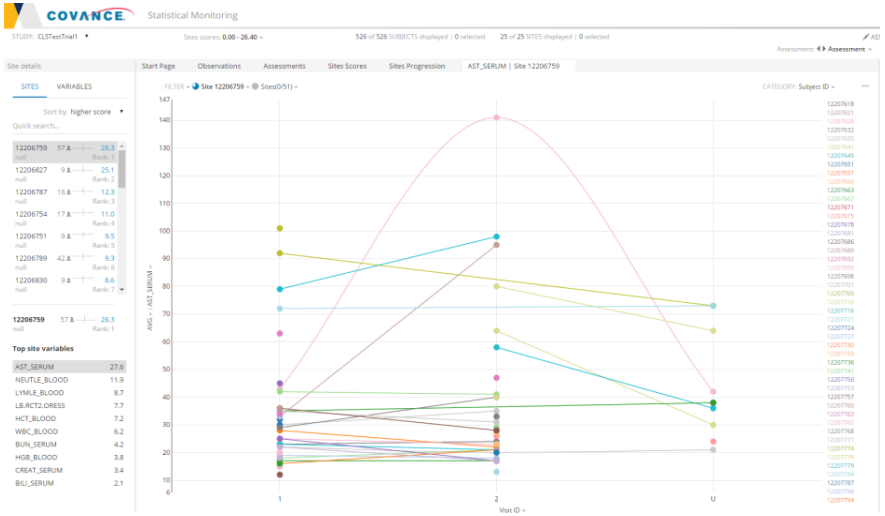
Statistical Review



Benefits

- Statistical detection of non-random anomalies in the distributions of clinical data that may be indicative of fraud, bias or sloppiness
- Statistical techniques combined with confirmatory graphics to facilitate interpretation
- Wide range of statistical tests including univariate data distributions, missing data frequency, event history, digit preference, unit (mis)use, trends over time, multivariate correlations, repeating values, autocorrelation, etc.





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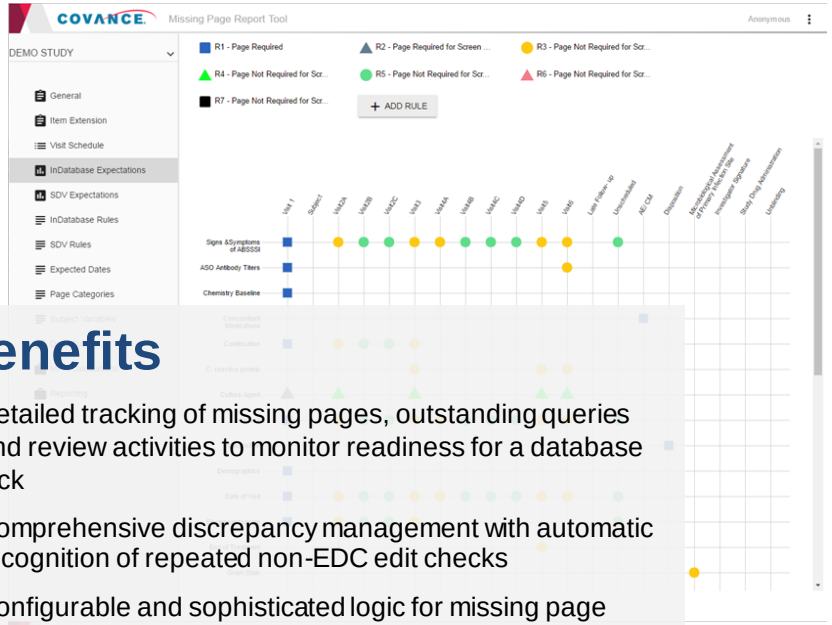
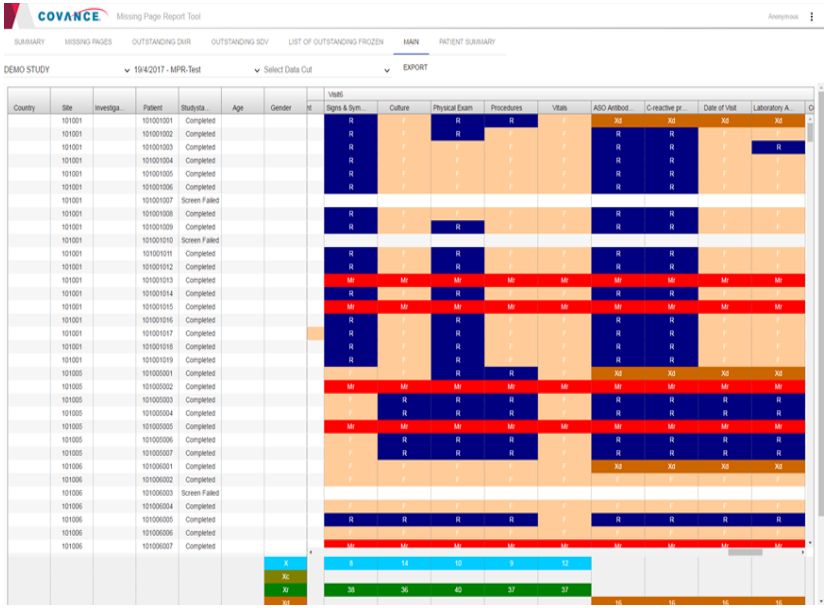
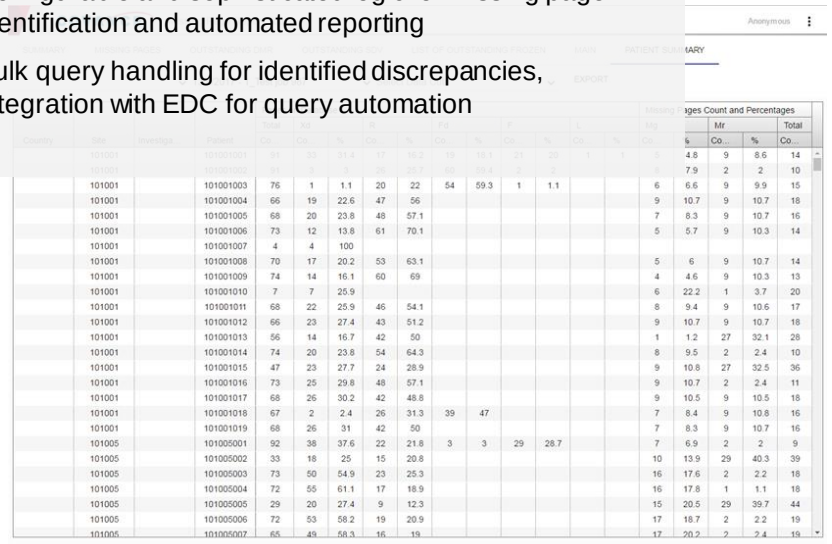
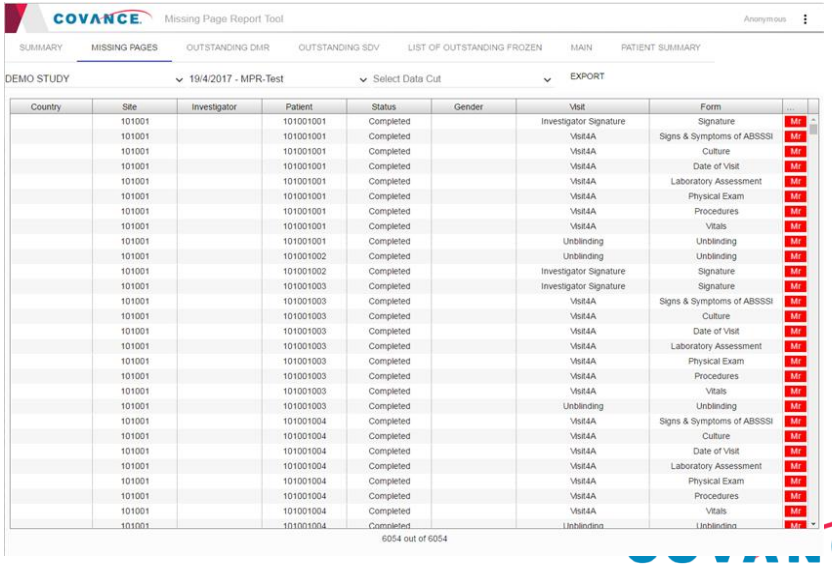
Data Review









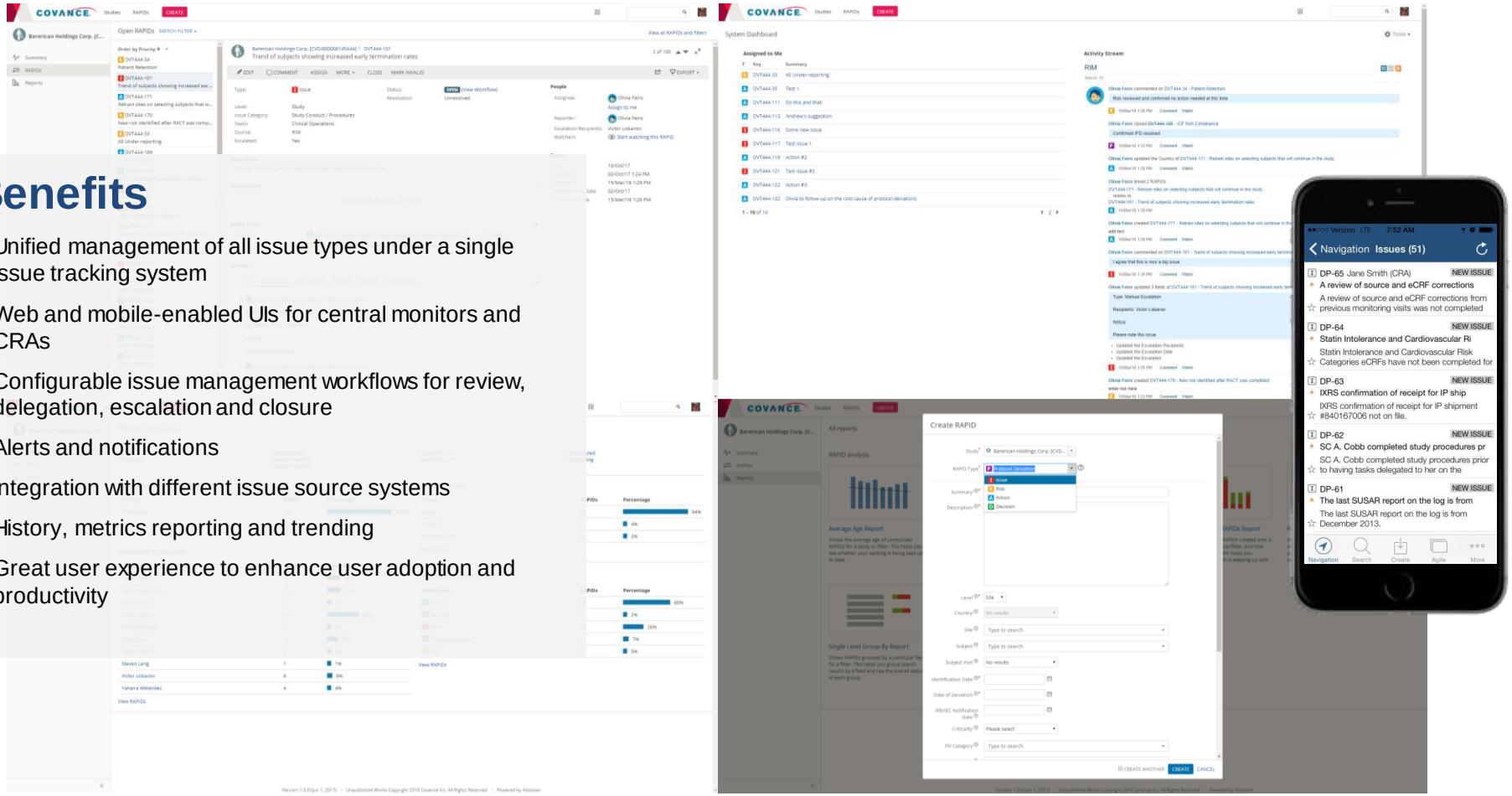
Benefits

- Detailed tracking of missing pages, outstanding queries and review activities to monitor readiness for a database lock
- Comprehensive discrepancy management with automatic recognition of repeated non-EDC edit checks
- Configurable and sophisticated logic for missing page identification and automated reporting
- Bulk query handling for identified discrepancies, integration with EDC for query automation

Risk and Issue Management

Benefits

- Unified management of all issue types under a single issue tracking system
- Web and mobile-enabled UIs for central monitors and CRAs
- Configurable issue management workflows for review, delegation, escalation and closure
- Alerts and notifications
- Integration with different issue source systems
- History, metrics reporting and trending
- Great user experience to enhance user adoption and productivity



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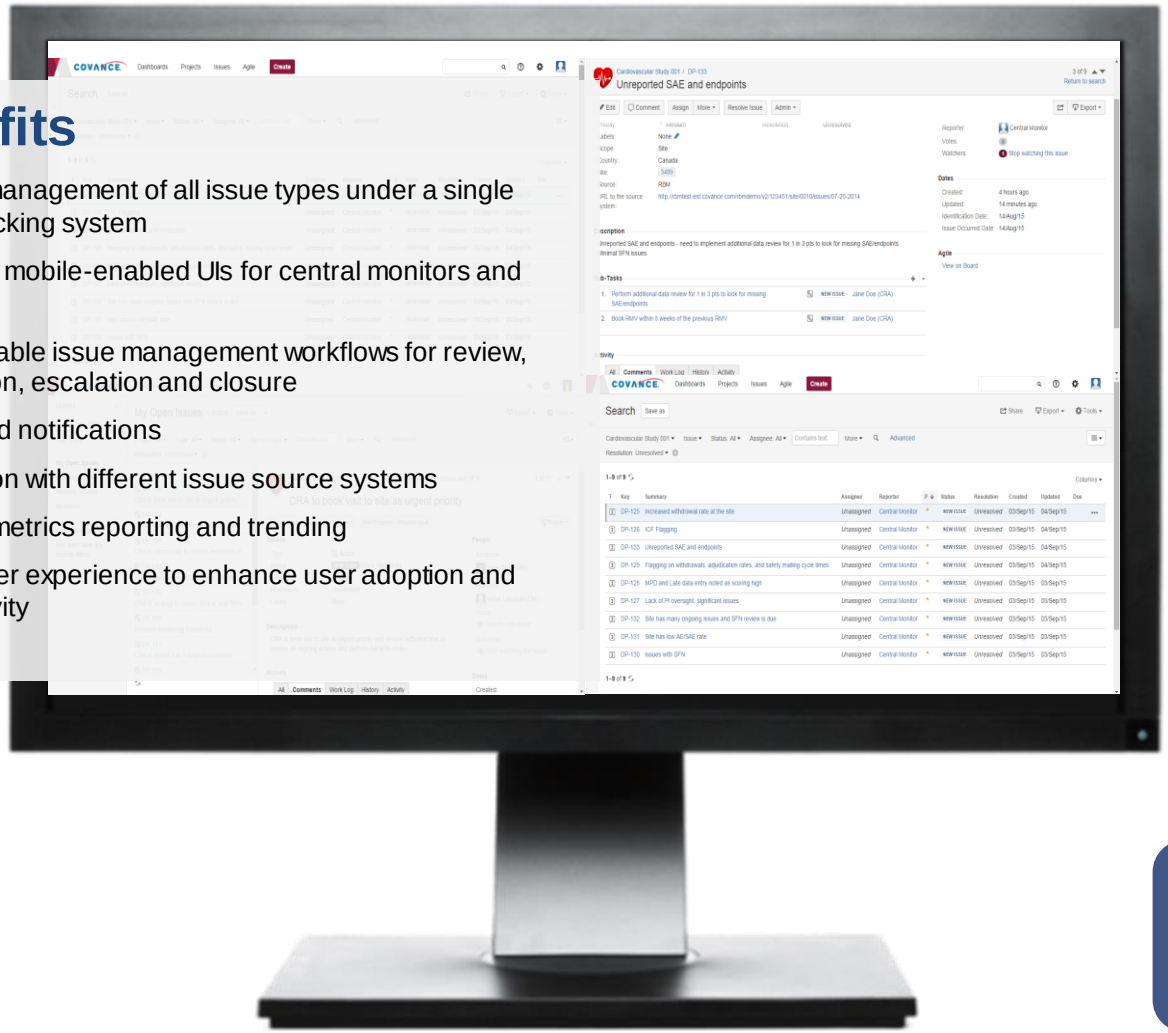

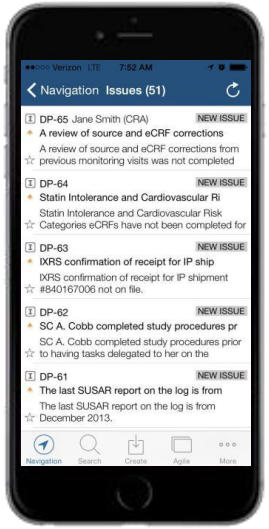

Tracks all study risks, issues and actions, sends notifications, enables workflows and reports

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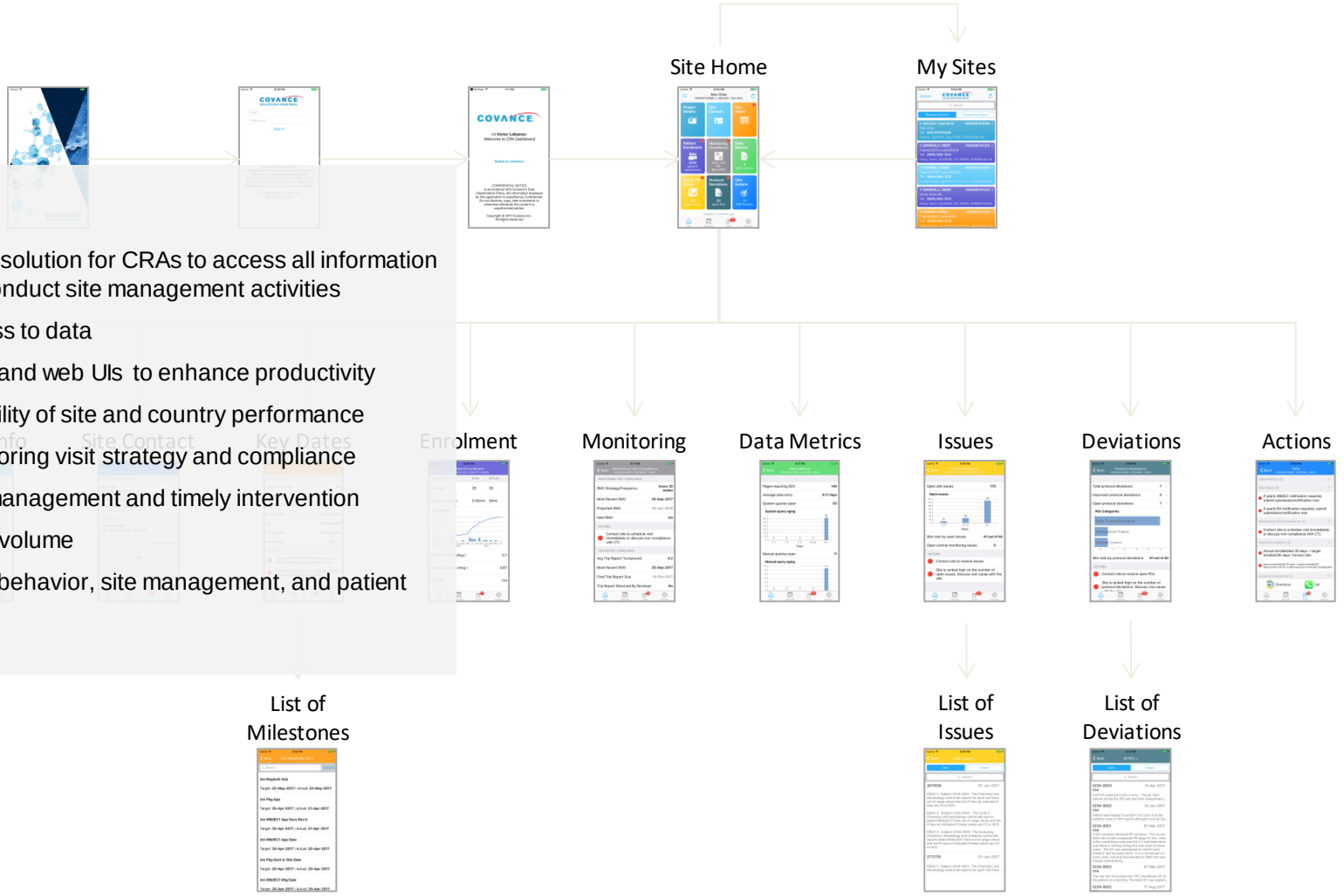
CRA Dashboard

Benefits

- One-stop-shop solution for CRAs to access all information necessary to conduct site management activities
- Real time access to data
- Elegant mobile and web UIs to enhance productivity
- Enhanced visibility of site and country performance
- Improved monitoring visit strategy and compliance
- Proactive risk management and timely intervention
- Reduced email volume
- Improved CRA behavior, site management, and patient care



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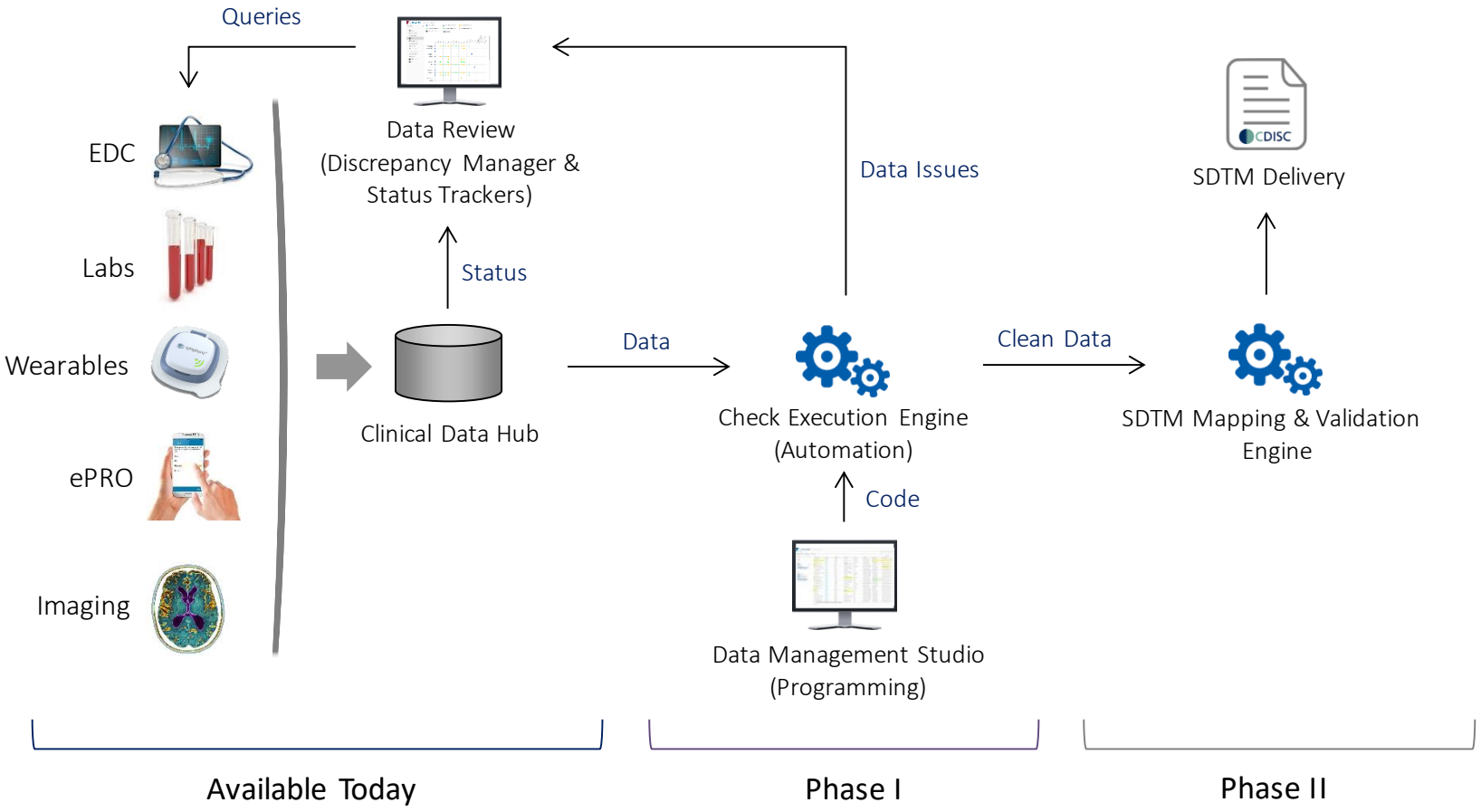
Data Management



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Enterprise SaaS Partnerships

Covance Announces Pioneering Agreement with Leading Pharmaceutical Company for Worldwide Portfolio-Level Clinical Trial Monitoring

Xcellerate® Monitoring sets new standard for risk-based monitoring of clinical trials

August 24, 2015 04:15 PM Eastern Daylight Time

PRINCETON, N.J.--(BUSINESS WIRE)--Laboratory Corporation of America® Holdings (LabCorp®) (NYSE: LH) today announced that Covance Drug Development (Covance) has received a multi-year award from a leading pharmaceutical company to use Covance's Xcellerate® platform as an exclusive central monitoring solution for their worldwide clinical trials portfolio. This landmark agreement with a top-tier pharmaceutical company for Covance's first-in-kind Software-as-a-Service (SaaS) offering reflects the company's unique technology capabilities, and reinforces its position as an industry innovator and leader in clinical informatics solutions.

Covance Enters into Strategic Technology Agreement with GSK

Leverages Covance's Xcellerate® Informatics Technology Across GSK's Global Clinical Trials Portfolio

February 28, 2018 04:40 PM Eastern Standard Time

BURLINGTON, N.C.--(BUSINESS WIRE)--LabCorp® (NYSE: LH), a leading global life sciences company, announced today that its Covance Drug Development (Covance) business has entered into a strategic technology agreement with GlaxoSmithKline plc (GSK). Under the terms of the agreement, GSK will use Covance's Xcellerate® Monitoring, Xcellerate Insights, and Xcellerate Clinical Data Hub solutions in a software-as-a-service (SaaS) model.

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Why Xcellerate

- **State-of-the-art SaaS solution** offering:
  - Unprecedented access to clinical trial data
  - Holistic assessment and mitigation of risk at the study, site and patient level
  - Early detection of problems, proactive risk management
  - Adaptive / tailored intervention depending on risk
  - Full transparency and oversight of CRO conduct and performance
  - Full state of control provable to regulators
- **Aligned with regulatory and ICH E6 guidelines**
- **Broadly applicable**, supporting multiple trial delivery paradigms, ideal for FSP
- **Informed and stress-tested** through our extensive real-world clinical trial experience
- **Extensively utilized** in our internally executed trials
- **Successfully implemented** at other leading pharma companies
- **Offered as a standalone service** decoupled from our clinical work
- **Platform-agnostic** allowing data integration with any source system
- **Priced competitively** to help sponsors contain costs and manage variability in study volume

Scattered Thoughts on AI and Hype

Hot Areas of AI

- Large-scale machine learning
  - Scaling of existing supervised and unsupervised learning algorithms to work with very large data sets
- Deep learning
  - Use of deep neural networks for audio, image, video, and language processing (speech, object, and activity recognition and labeling)
- Reinforcement learning
  - Enhanced pattern recognition techniques to support experience-driven sequential decision-making and ability to take actions in the real world
- Computer vision
  - Most mature area of AI and most transformed by deep learning; current research is focused on automatic image and video captioning
- Robotics
  - Training robots to interact with the world around it in generalizable and predictable ways; heavy reliance on computer vision and other forms of machine perception
- Natural language processing
  - Ability to interpret and translate written and spoken language, with increasing emphasis on enabling machines to engage in a dialog with humans
- Collaborative systems
  - Autonomous systems that can utilize the complementary strengths of humans and machines and work collaboratively with other systems and with humans
- Crowdsourcing and human computation
  - Methods to enable computer systems to make automated calls to human expertise to solve problems that computers alone cannot solve well
- Algorithmic game theory and computational social choice
  - Distributed, multi-agent systems to address economic and social dimensions, such as handling potentially misaligned incentives, including self-interested human participants or firms and the automated AI-based agents representing them
- Internet of things
  - Use of interconnected devices that can collect and share their abundant sensory information to use for intelligent purposes
- Neuromorphic computing
  - Technologies that seek to mimic biological neural networks to improve the hardware efficiency and robustness of computing systems, often replacing the traditional emphasis on separate modules for input/output, instruction-processing, and memory

AI Applications in Life Sciences

- Drug discovery (target selection, lead generation / optimization, …)
- Biomarker selection and imaging
- Disease identification and diagnosis
- Disease prevention
- Personalized treatment, behavioral modification
- Clinical trial design, protocol optimization
- Feasibility and site selection
- Patient recruitment
- Patient monitoring
- Data acquisition (EMR)
- Data management
- Risk management and mitigation
- Medication adherence
- Voice of the patient, social listening
- Clinical decision support
- Portfolio management

AI Challenges

- Creating safe and reliable hardware for sensing and effecting
- Interacting smoothly with human experts
- Overcoming fears of marginalizing humans
- Quantifying and minimizing impact of errors
- Gaining public trust
- Living up to the hype

Thank You

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