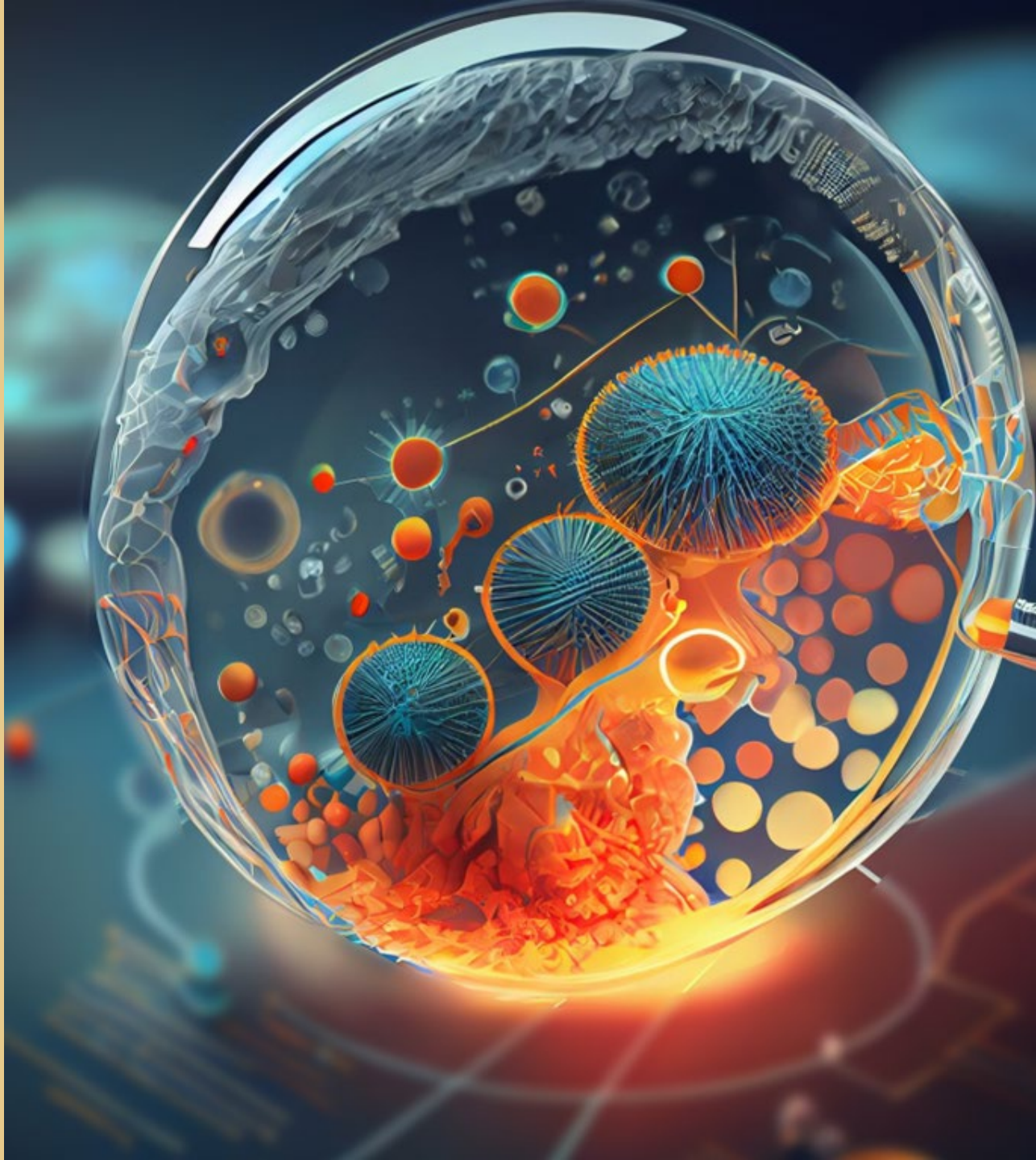
eha Sf(PM)

Computational approaches to precision medicine

Breakout Session 6C

Aedin Culhane, Kasper Karlsson, Jesse Boehm, Sanju Sinha, Jing Tang

26.09.2024



Panel members

Aedin Culhane, University of Limerick, Ireland

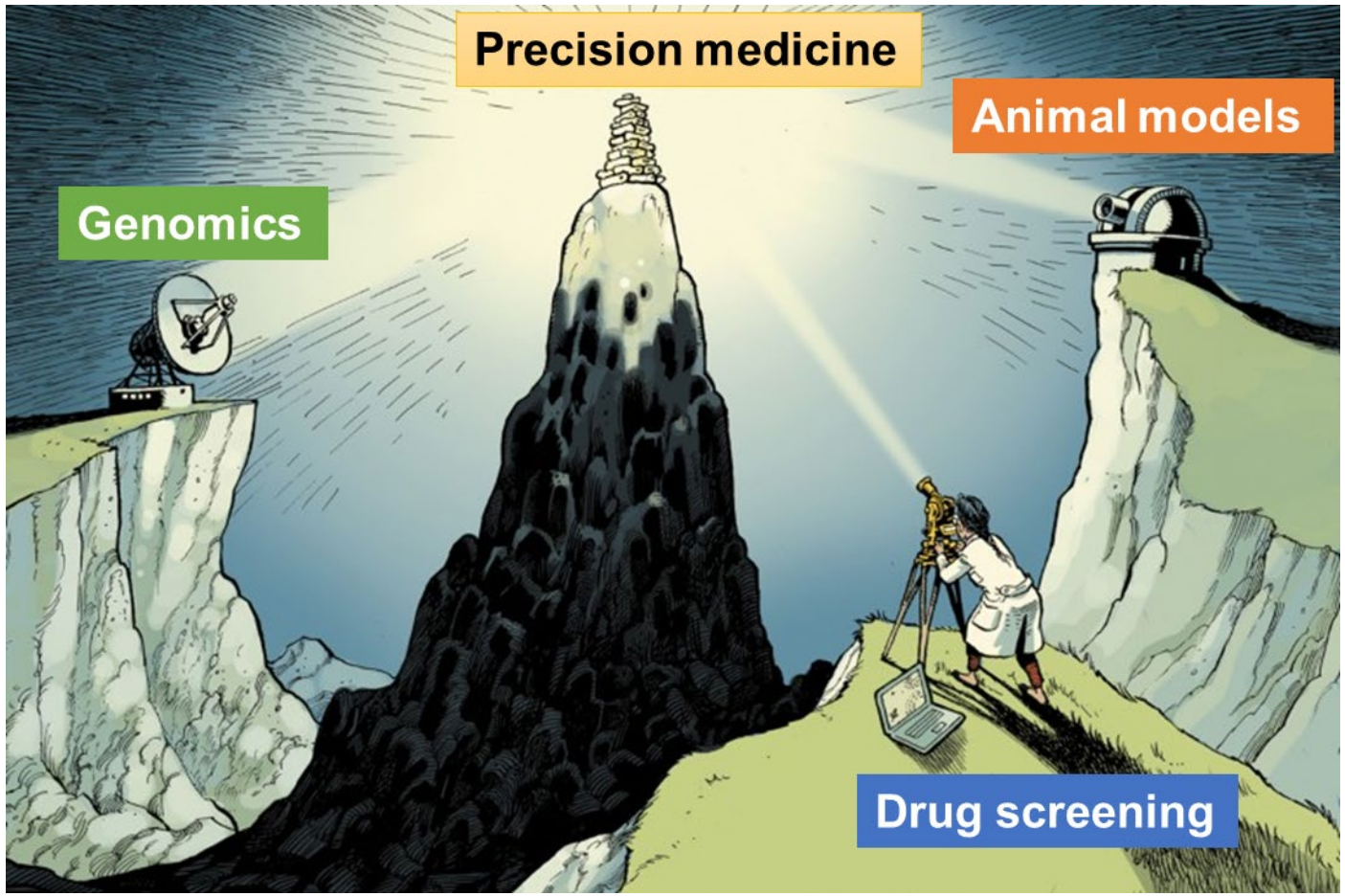
Kasper Karlsson, Karolinska Institutet, Sweden

Jesse Boehm, MIT's Koch Institute, USA

Sanju Sinha, Sanford Burnham Prebys Medical Discovery Institute, USA

Jing Tang, University of Helsinki, Finland

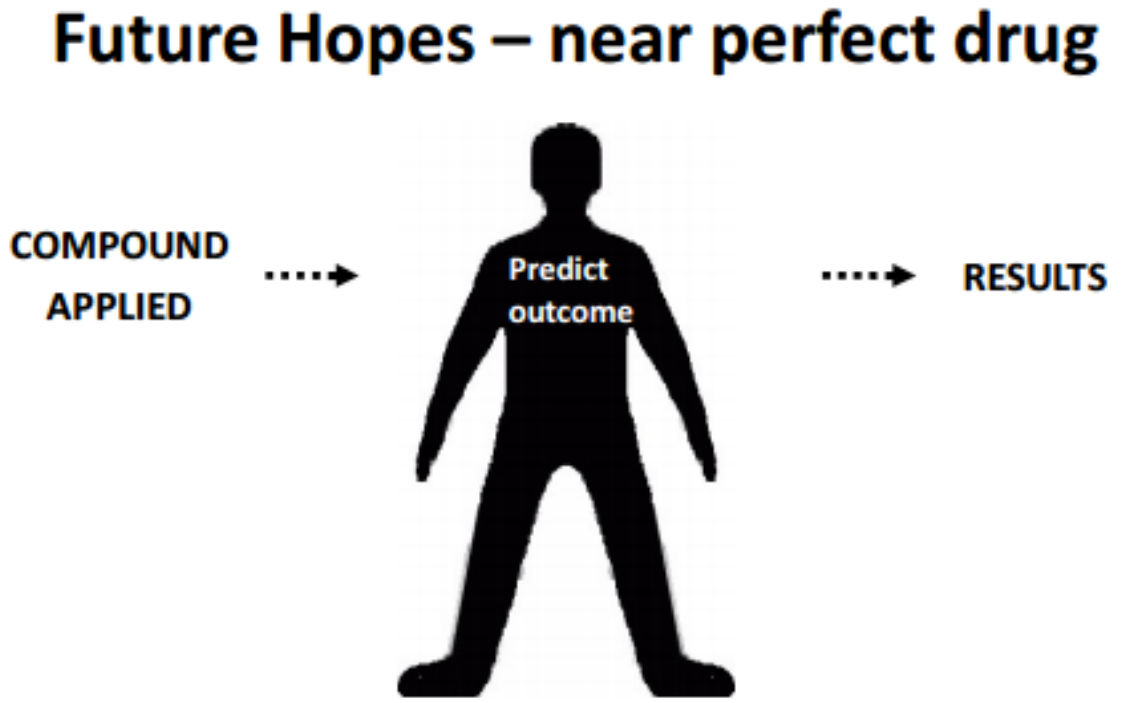
How to achieve precision medicine?



Nature 553, 399-401 (2018)

Grand challenges in precision medicine

How to make it happen?



Discussion topics

01 The state-of-the-art of computational approaches

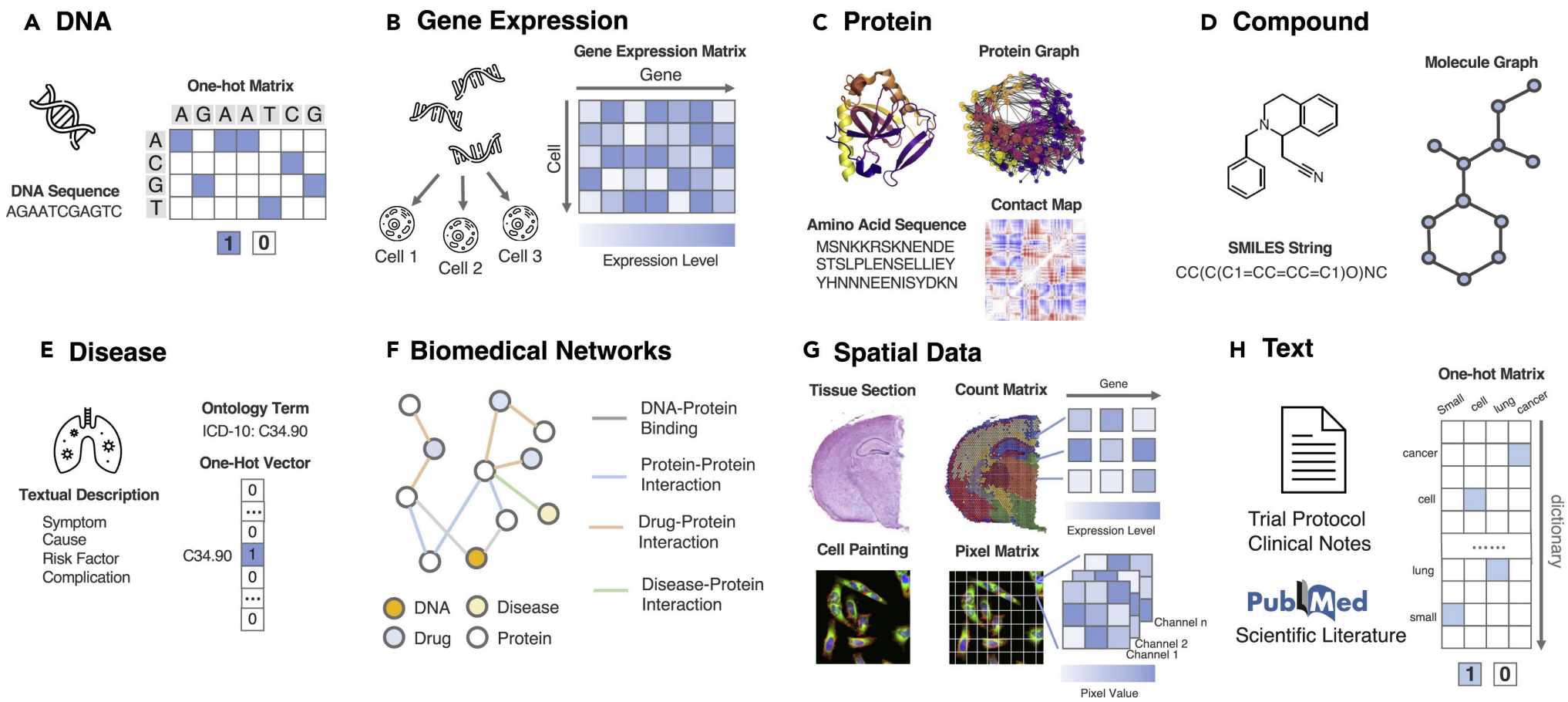
02 Computational complexity versus biological complexity

03 Interpretability and transferability of computational approaches

04 Challenges and benefits of federated versus centralized approaches

05 Implementation in the clinics

Modalities in precision medicine



Patterns, 2021, 2(10):100328.

eha Sf(PM)

1. The state-of-the-art computational approaches

A How can we effectively integrate multi-omics data?

B How do we account for tumor heterogeneity in predictive models?

C What are the best methods to predict drug resistance?

2. Computational versus biological complexity

Science Translational Medicine

Cover story: Many drugs miss the mark

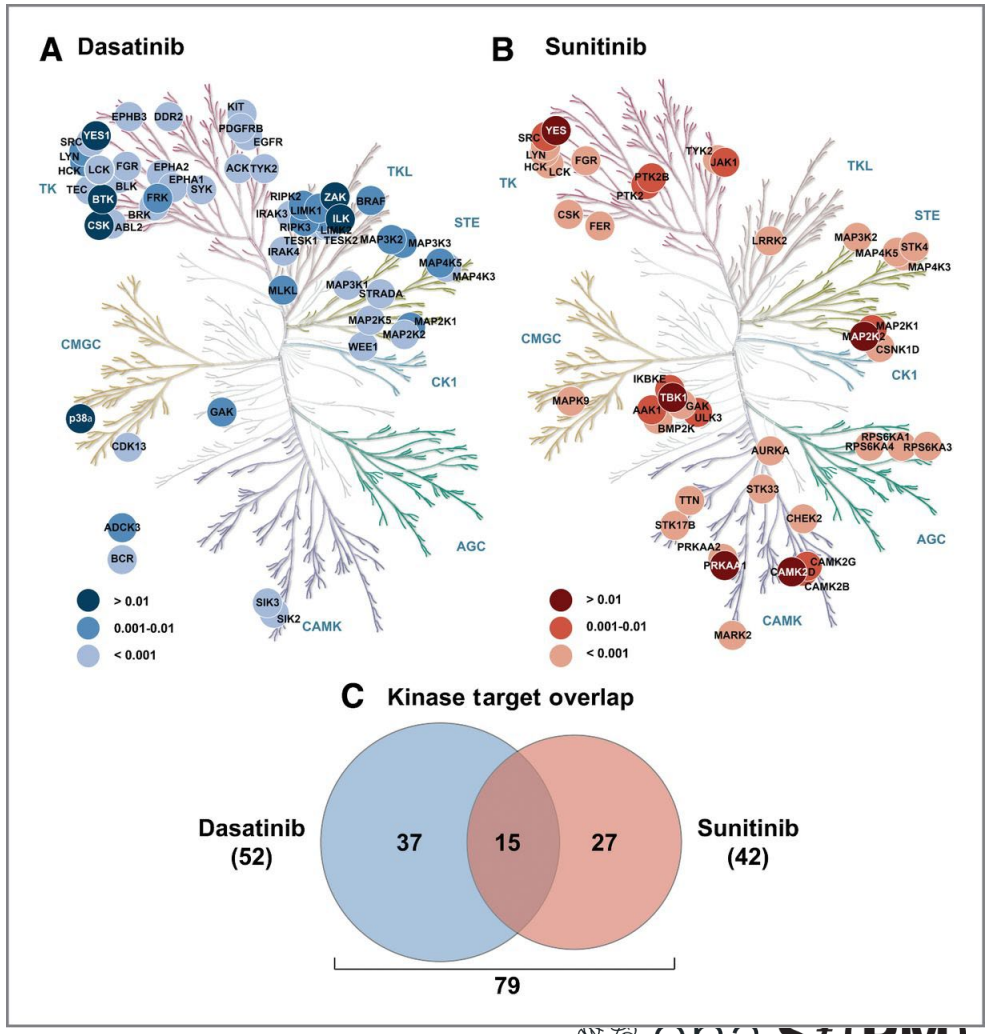
CRISPR screening reveals that many oncogene targets are dispensable for cell proliferation and identifies the true target of one mischaracterized drug

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Off-target toxicity is a common mechanism of action of cancer drugs undergoing clinical trials

Ann Lin[1,2]*, Christopher J. Giuliano[1,2]*, Ann Palladino[1], Kristen M. John[1,3], Connor Abramowicz[1,4],



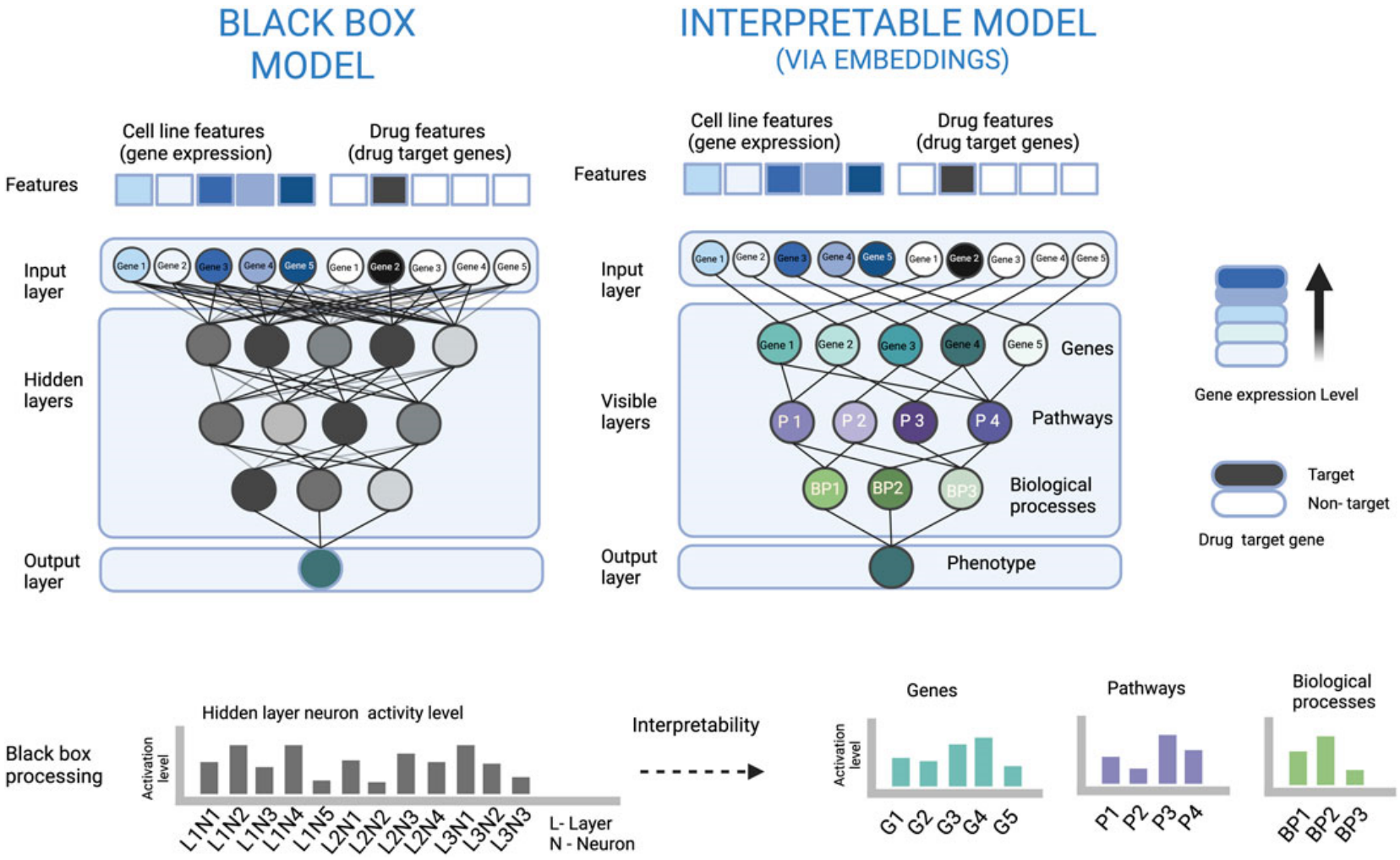
2. Computational versus biological complexity

A How can we optimize computational algorithms for patient-specific modeling?

B How can uncertainty quantification be implemented without adding excessive computational complexity?

C How can we balance the trade-off between detailed mechanistic modeling and computationally efficient abstraction?

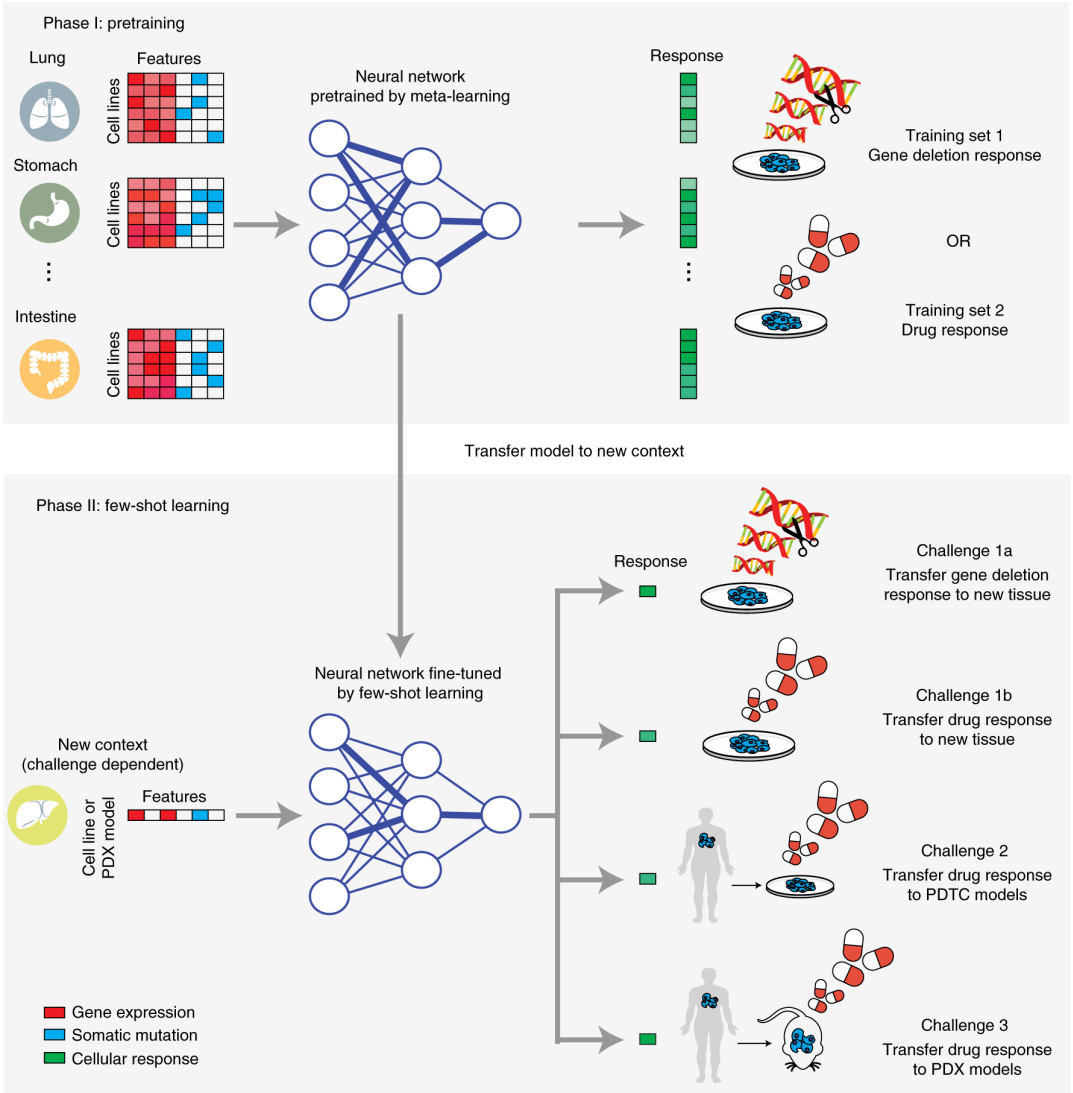
Interpretability versus transferability



Front Bioinform. 2022 Nov 17:2:1036963

eha Sf(PM)

Interpretability versus transferability



Nat Cancer **2**, 233–244 (2021)

eha Sf(PM)

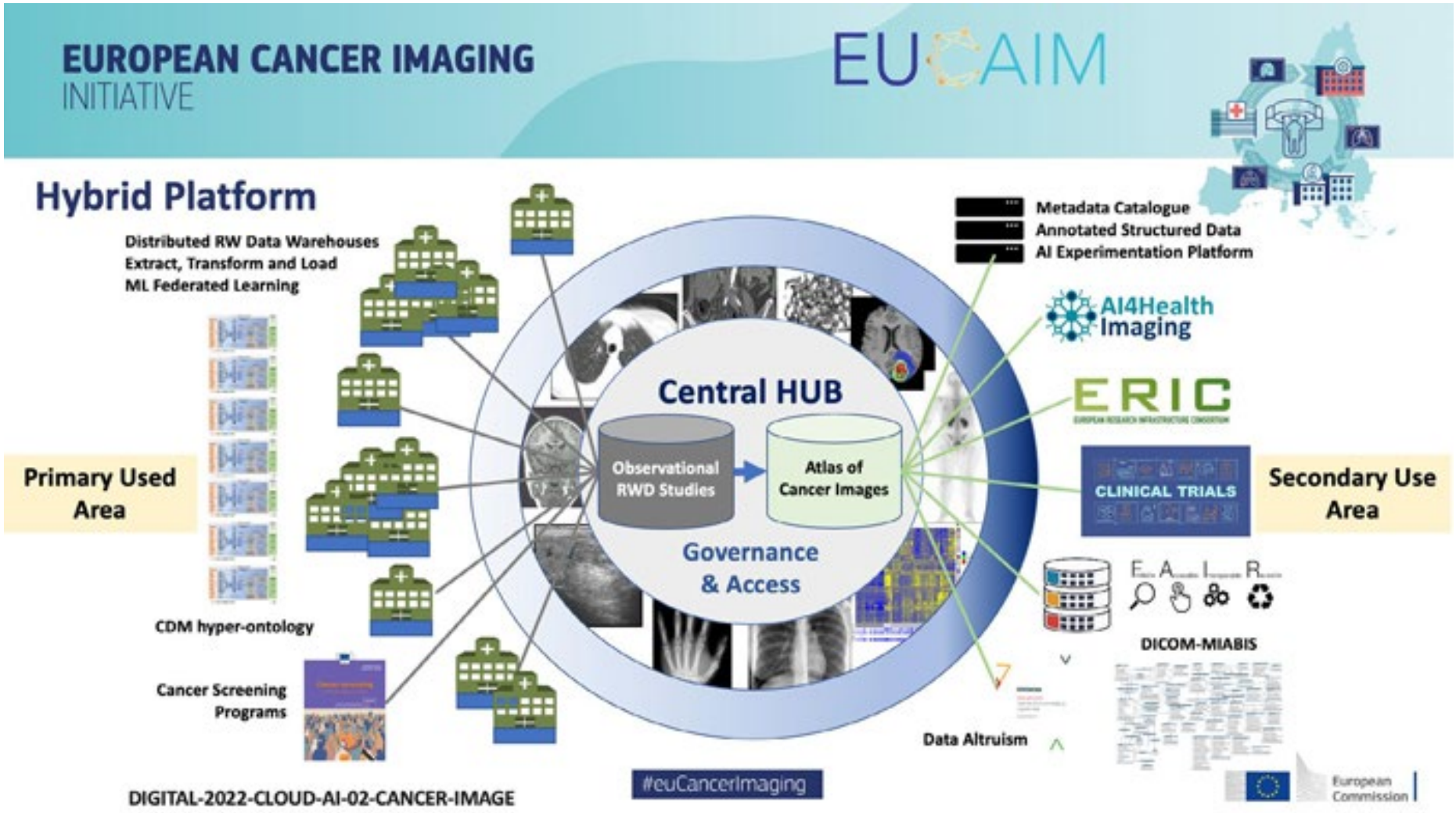
Interpretability versus transferability

A Complex Models Often Lack Interpretability?

B Enhancing the transferability of models often involves making them more complex?

C How do we ensure that computational models generalize well across different biological contexts?

Federated versus centralized approaches



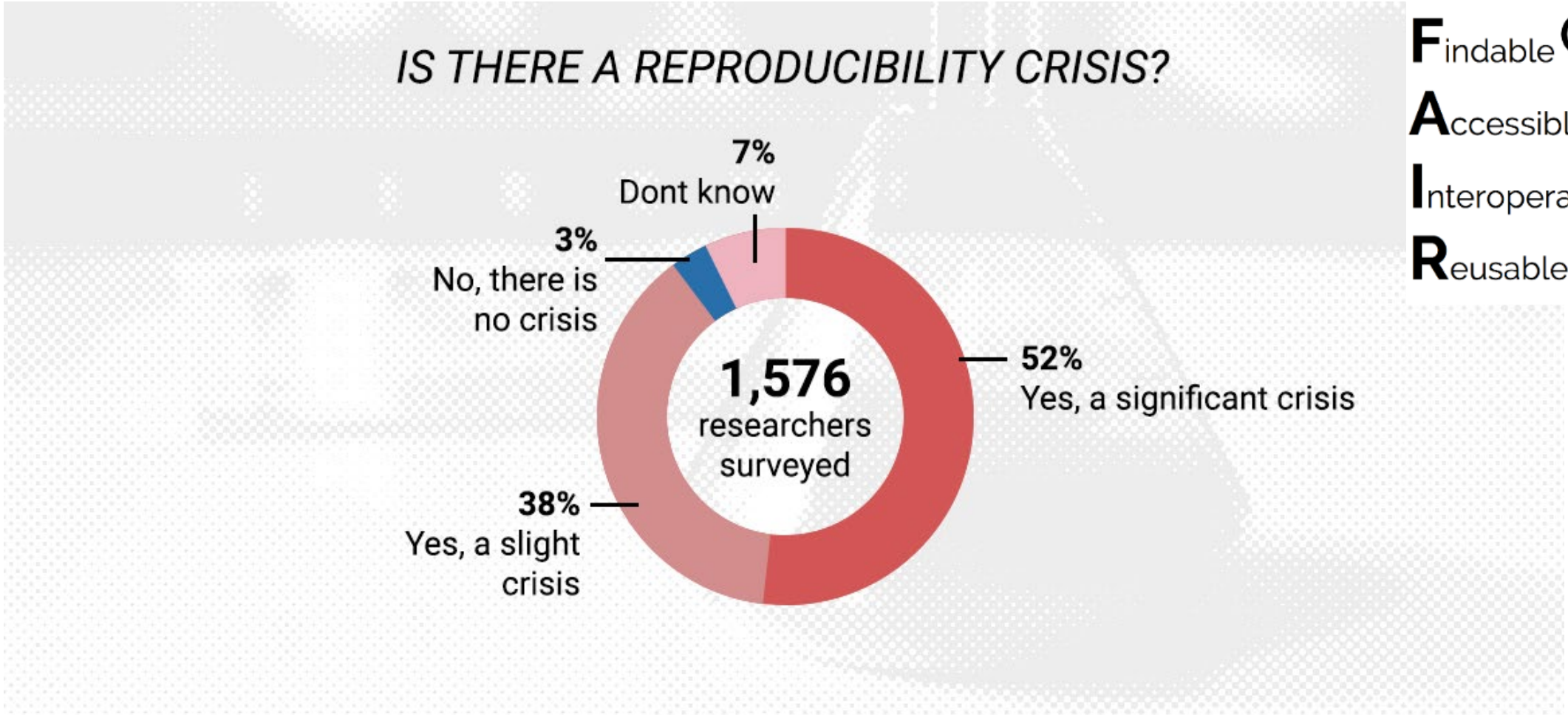
Federated versus centralized approaches

A Data Standardization and Interoperability

B How can federated systems ensure secure data communication between institutions?

C Can centralized systems handle the enormous computational power required for analyzing large-scale, multi-omics, and clinical data from diverse sources?

Implementation and deployment



Findable
Accessible
Interoperable
Reusable

Nature **533**, 452–454 (2016)

eha Sf(PM)

Implementation and deployment

Table 2.

Outcomes of the initial 27 substudies (of 38 total) in NCI-MATCH.

Arm	Molecular Aberration	Treatment	N Enrolled	N Evaluable[†]	Number of Responses (%)	6-month PFS	Ref	Met Endpoint?[*]
A	EGFR activating mutations	afatinib	19	14	1 (7.1%)	8.9%	18	No
B	HER2 activating mutations	afatinib	40	37	1 (2.7%)	12.0%	19	No
F	**ALK fusions**	**crizotinib**	**5**	**4**	**2 (50.0%)**	**25%**	**20**	**Yes**
G	ROS1 fusions	crizotinib	4	4	1 (25.0%)	50%	20	No
H	**BRAF V600E or V600K mutations**	**Dabrafenib/ trametinib**	**35**	**29**	**11 (37.9%)**	**68.4%**	**21**	**Yes**
I	PIK3CA mutation without RAS mutation or PTEN loss	taselisib	70	61	0.0%	19.9%	22	No
J	HER2 amplification	Trastuzumab/ pertuzumab	35	25	3 (12%)	25.3%	23	No
K2	**FGFR mutation/ fusion**	**erdafitinib**	**35**	**21**	**3 (14.3%)**	**36.8%**	**24**	**Yes**
M	TSC1 or TSC2 Mutations	TAK-228	49	34	5 (14.7%)	28.7%	25	No
N	PTEN aberration, with + expression on IHC	GSK2636771	24	22	0.0%	4.8%	26	No
P	PTEN loss by IHC	GSK2636771	35	32	0.0%	3.3%	26	No
Q	HER2 amplification	ado-trastuzumab emtansine	38	36	2 (5.6%)	23.6%	27	No

Nat Med. 2023, 29(6): 1349–1357

Implementation and deployment

A How can we ensure scalable, reproducible computational methods for large-scale clinical applications?

B How can we incorporate real-world evidence (RWE) into predictive models?

C Real-Time Integration and Decision Support

What have we learned

Reward bioinformaticians

Biological data will continue to pile up unless those who analyse them are recognized as creative collaborators in need of career paths, says **Jeffrey Chang**.

Nature **520**, 151–152 (2015)