network medicine: what do we learn from co-morbidity networks?

stefan thurner

with

Peter Klimek, Silke Aichberger, Anna Chmiel, Nina Haug, Caspar Matzhold, Sarah Etter, Ruggiero Lo Sardo, Michaela Kaleta, Johannes Sorger

Alexandra Kautzky-Willer, Gottfried Endel, Miriam Leitner, Irmgard Schiller-Frühwirth, Thomas Niederkrotenthaler, Ellenor Mittendorfer-Rutz, Michael Leutner

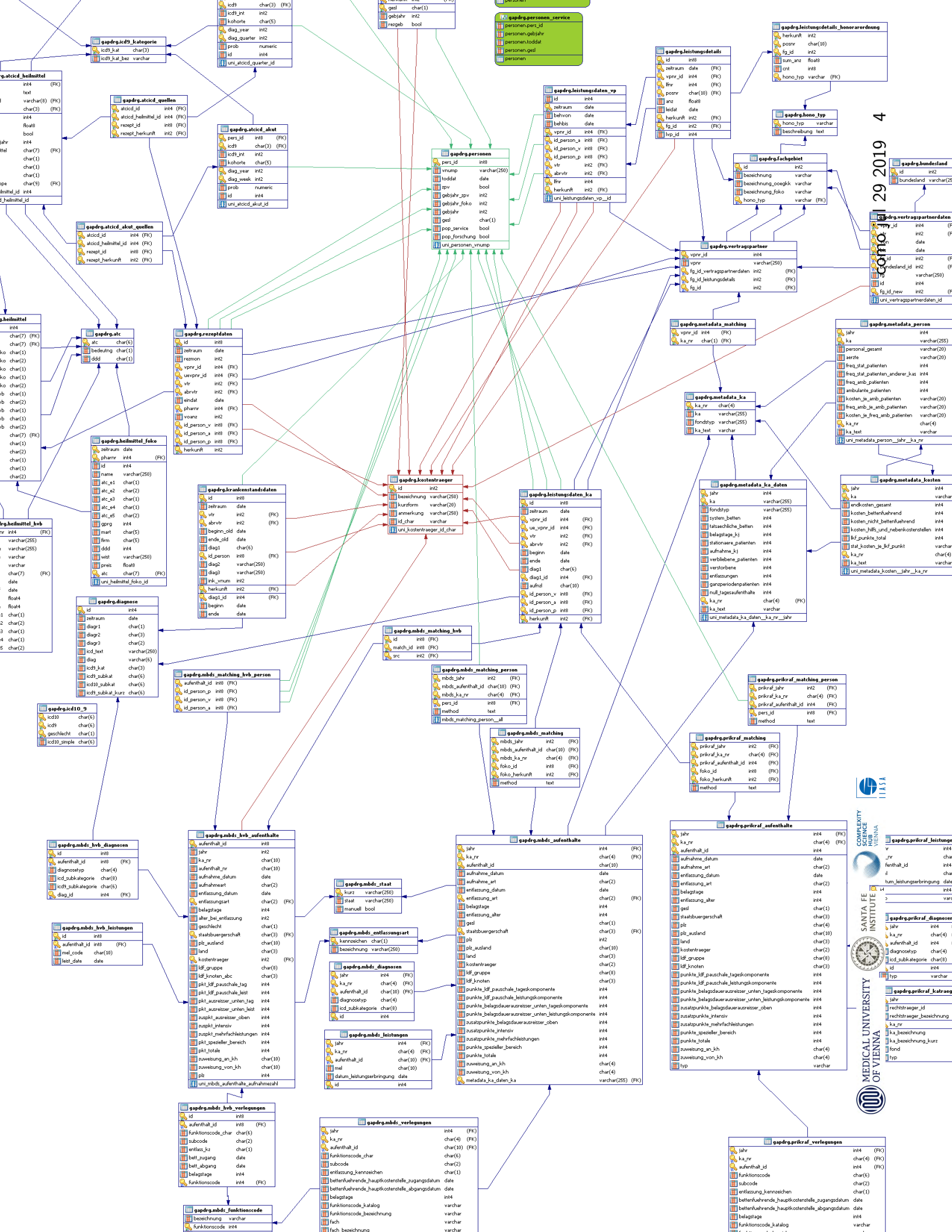
support by

FP7, H2020, WWTF, FFG, Hauptverband SV

National medical claims data

every paid **health service** $\rightarrow$ **one** data line

date — patient ID — healthcare practitioner ID — diagnosis — side diagnosis — prescription — price if generic drug/treatment/therapy — pharmacy ID — price of medication — date of purchase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COMPLEXITY SCIENCE HUB VIENNA
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MEDICAL UNIVERSITY OF VIENNA

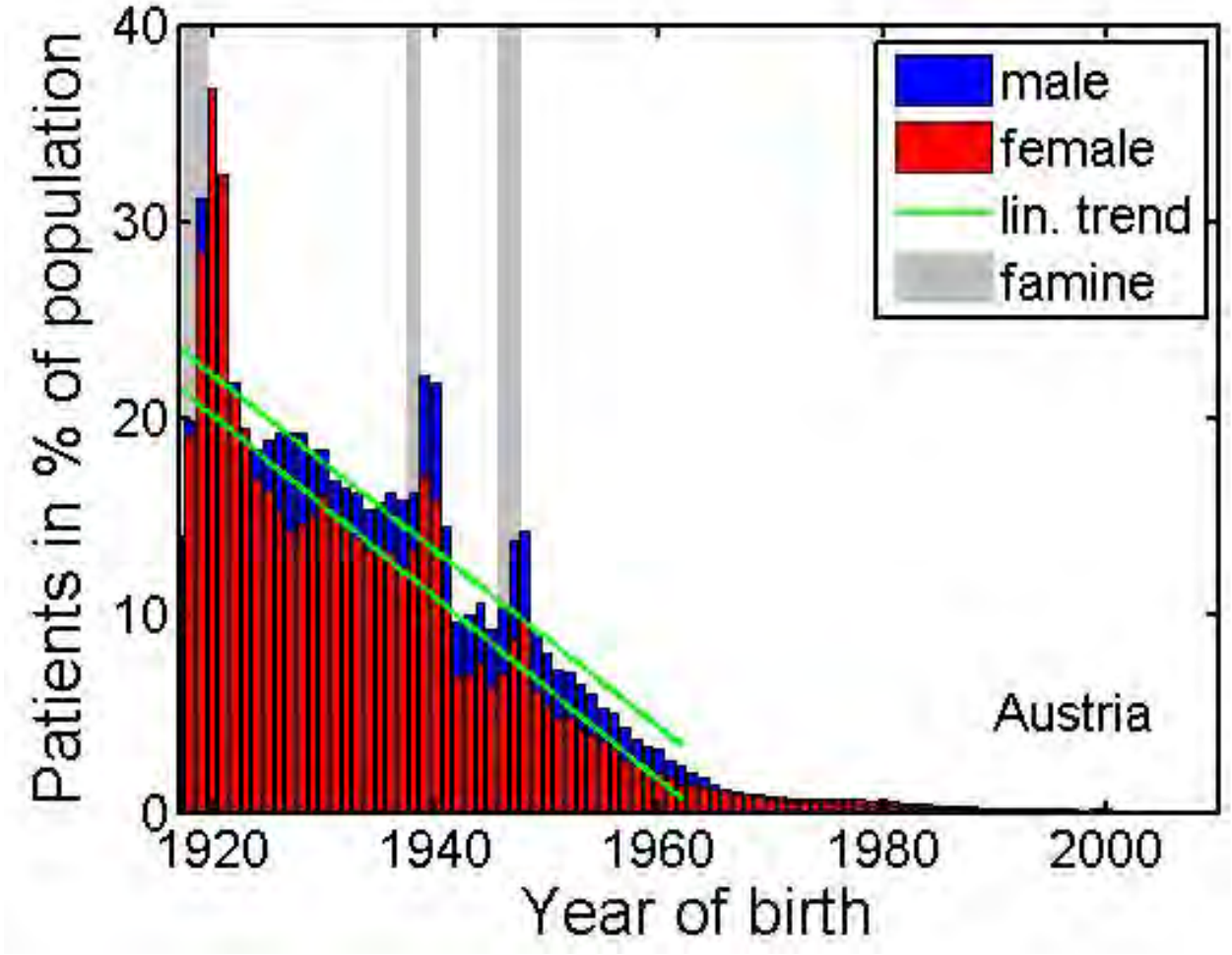
100.000.000 data-lines / year

The data

- 8,000,000 patiens
- 100,000,000 patient contacts per year
- 2,000,000 hospitalizations per year
- 12,000 health care providers
- 6,102 diseases (ICD10 code)
- 1,171 substances (ATC code)
- 255 hospitals
- 1,238 pharmacies

How sick are Austrians?

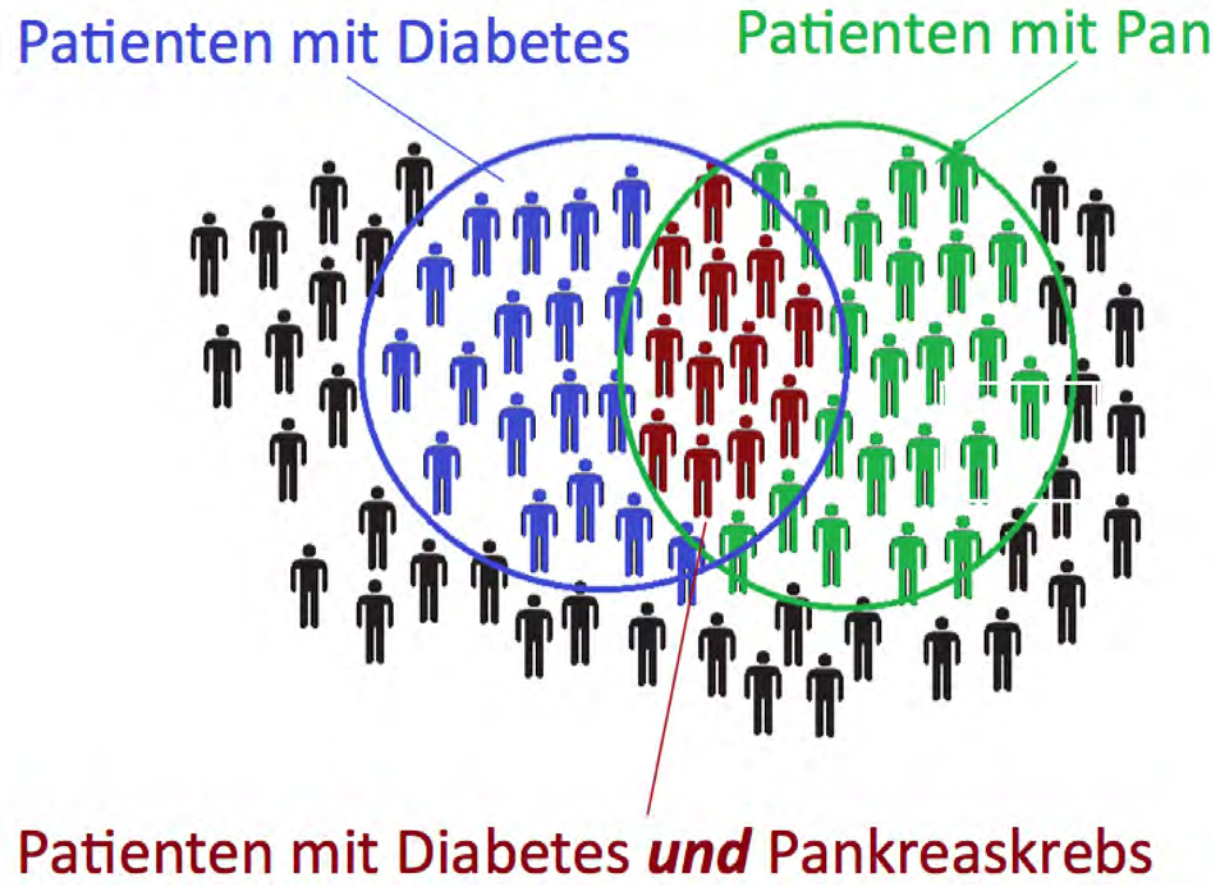
Epigenetics of diabetes
take all 300.000 diabetes patients

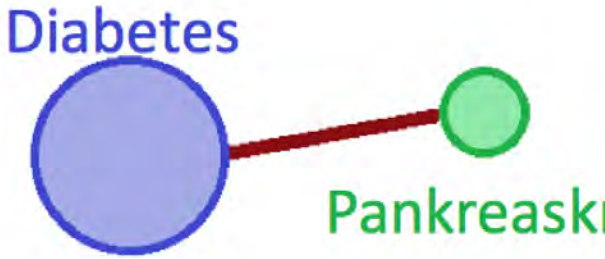


malnutrition during pregnancy $\rightarrow$ baby develops diabetes

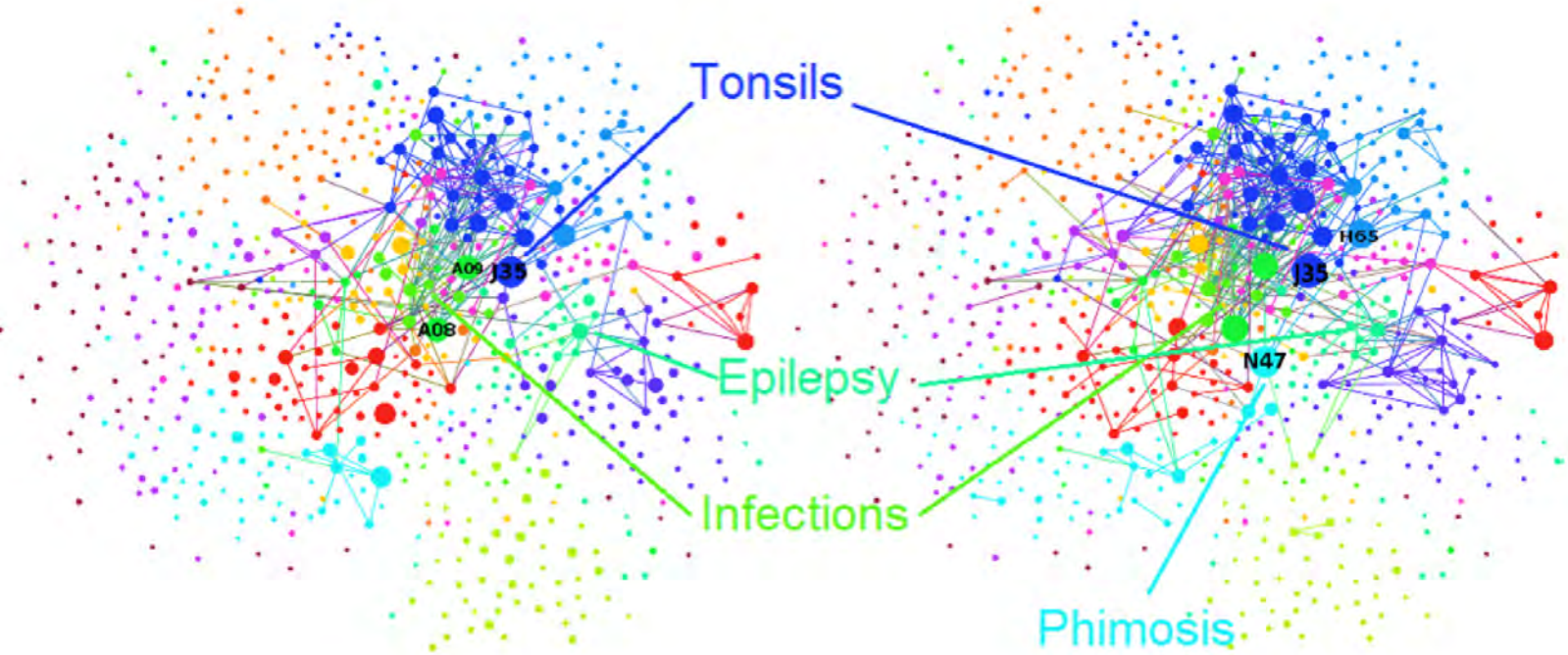
S Thurner et al. PNAS 110, 4703-4707 (2013)

How sick are Austrians?





Comorbidity network Austrians



females

- A and B - Certain infectious
- C - Neoplasms
- D - Benign neoplasms and blood diseases
- E - Endocrine, nutritional and metabolic diseases
- F - Mental and behavioural disorders
- G - Diseases of the nervous system
- H - Diseases of the eye and ear
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males

- L - Diseases of the skin and subcutaneous tissue
- M - Diseases of the musculoskeletal system
- N - Diseases of the genitourinary system

0-8 Jahre
9-16 Jahre
17-24 Jahre
25-32 Jahre
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41-48 Jahre
49-56 Jahre
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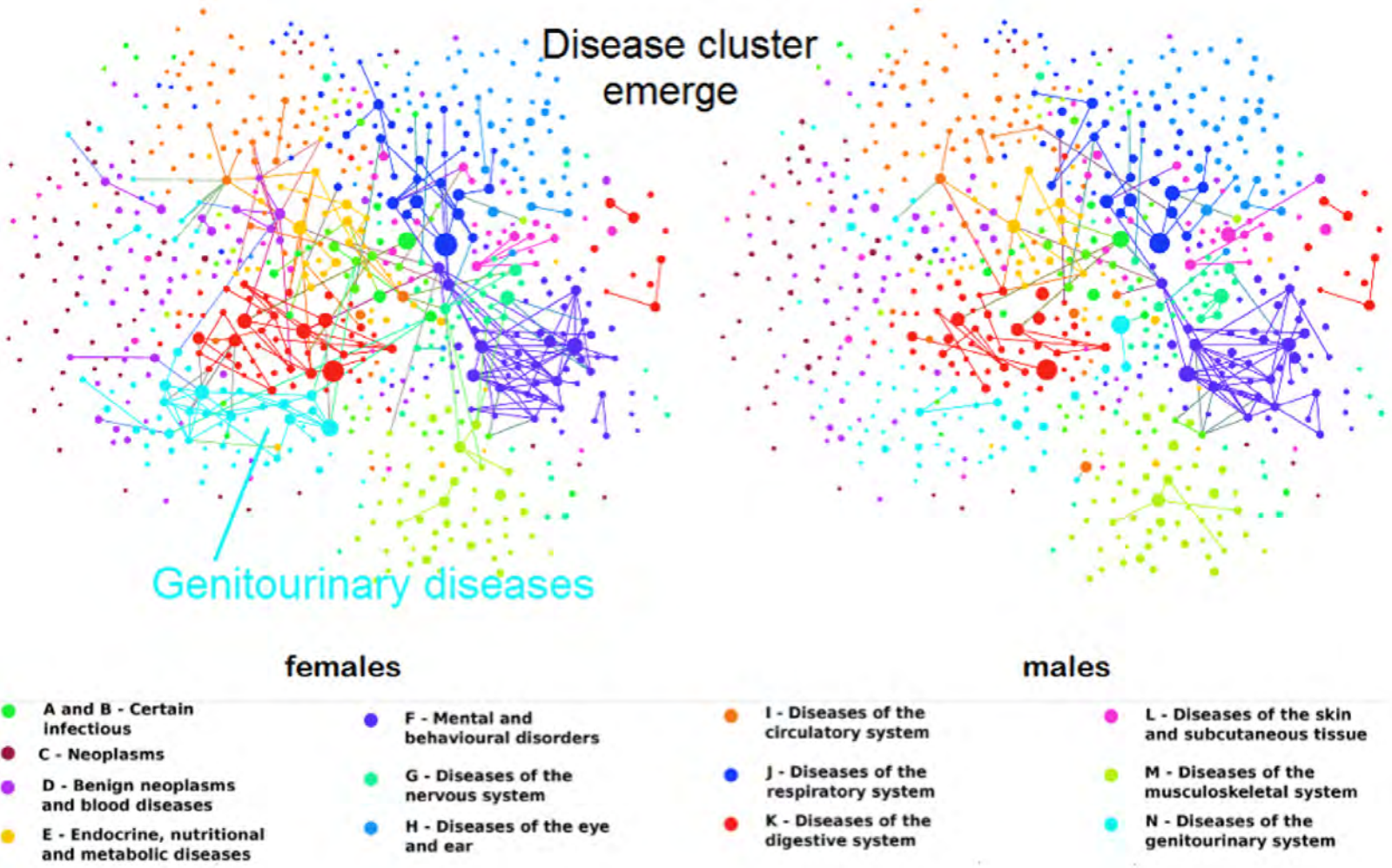

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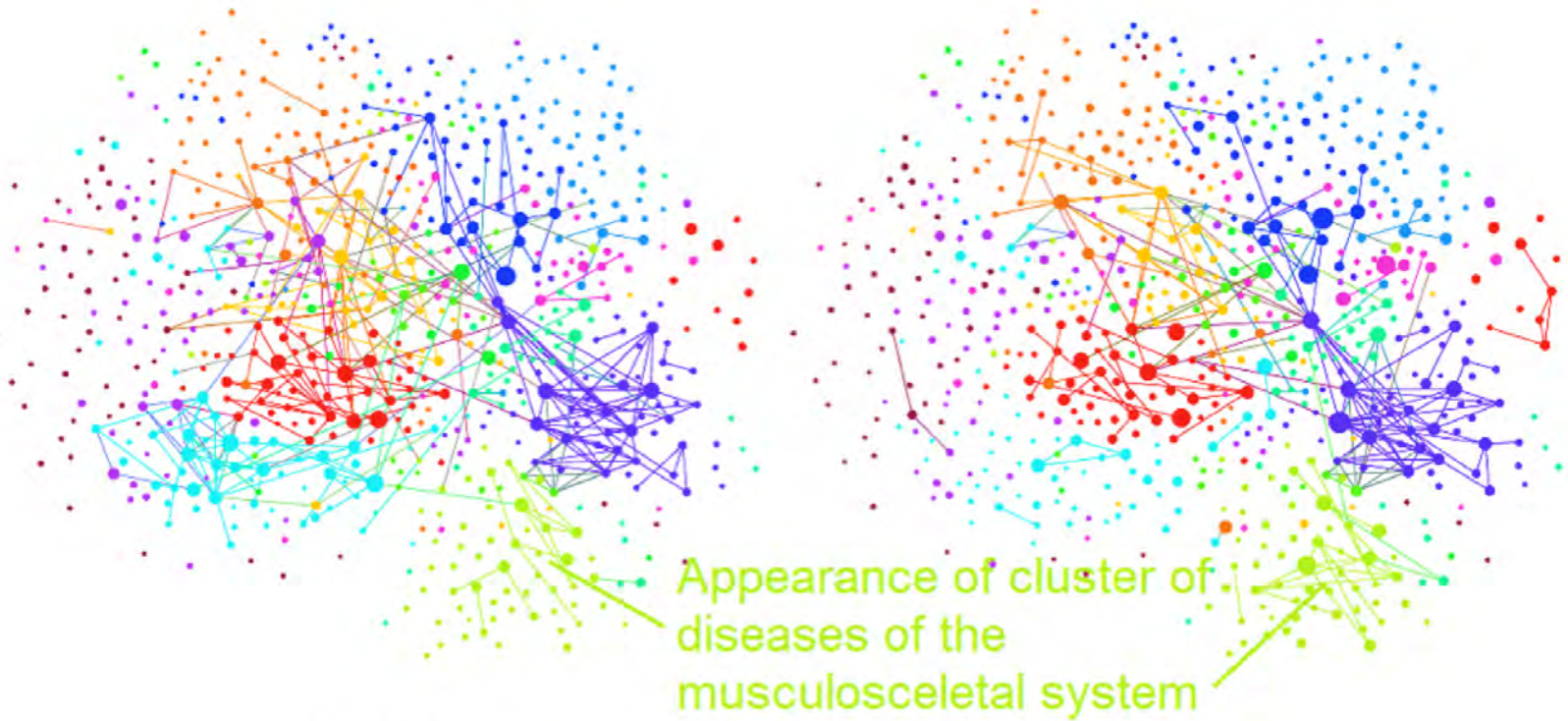

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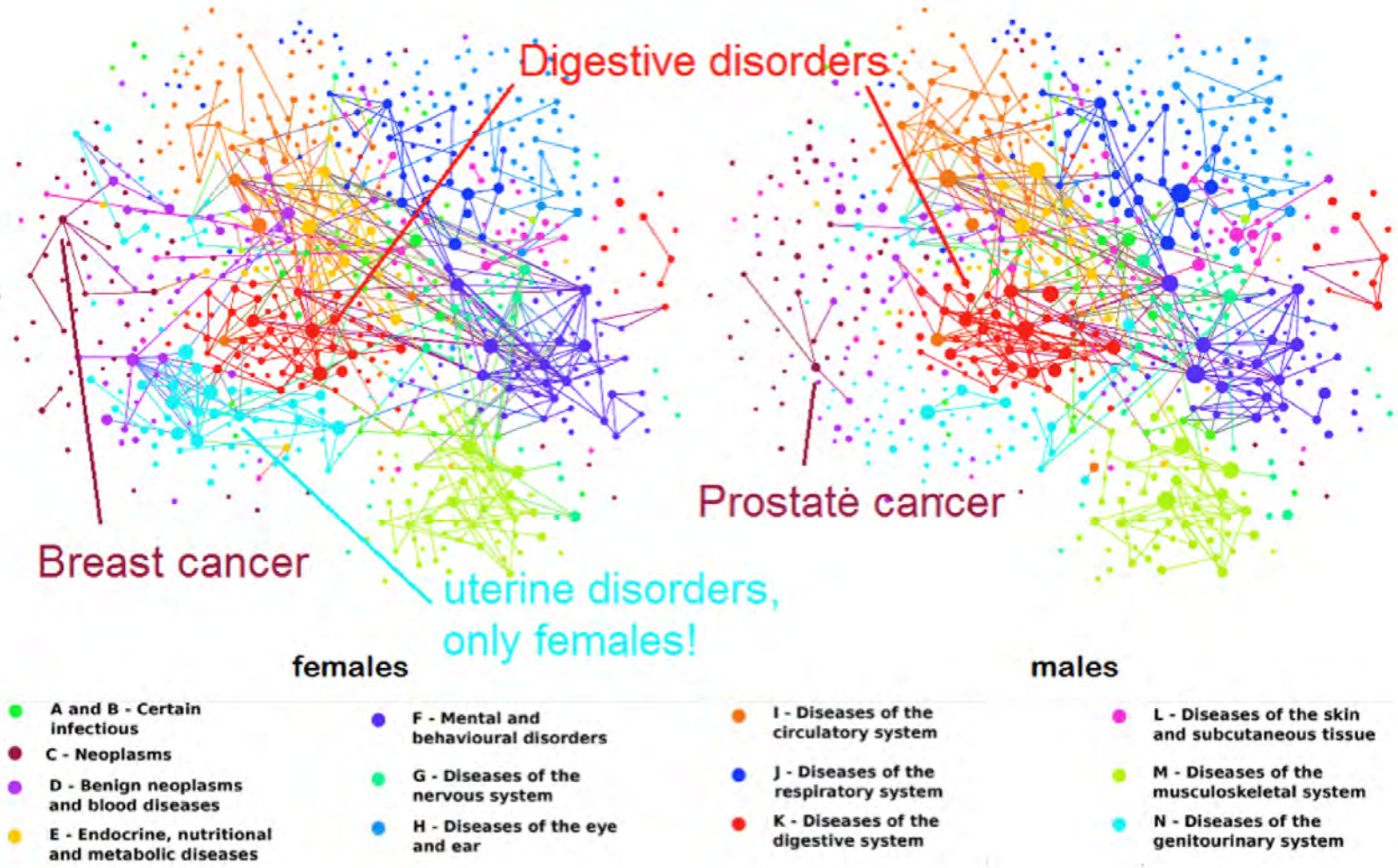

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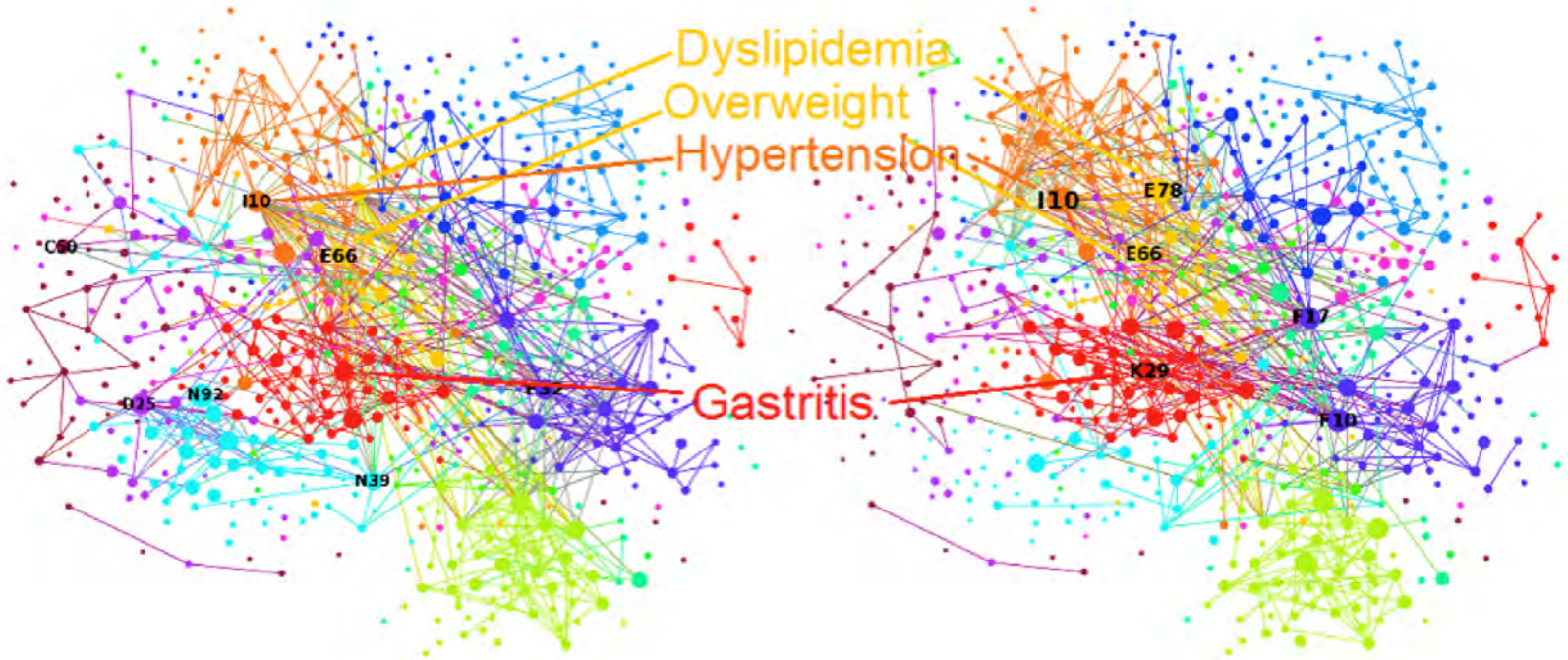

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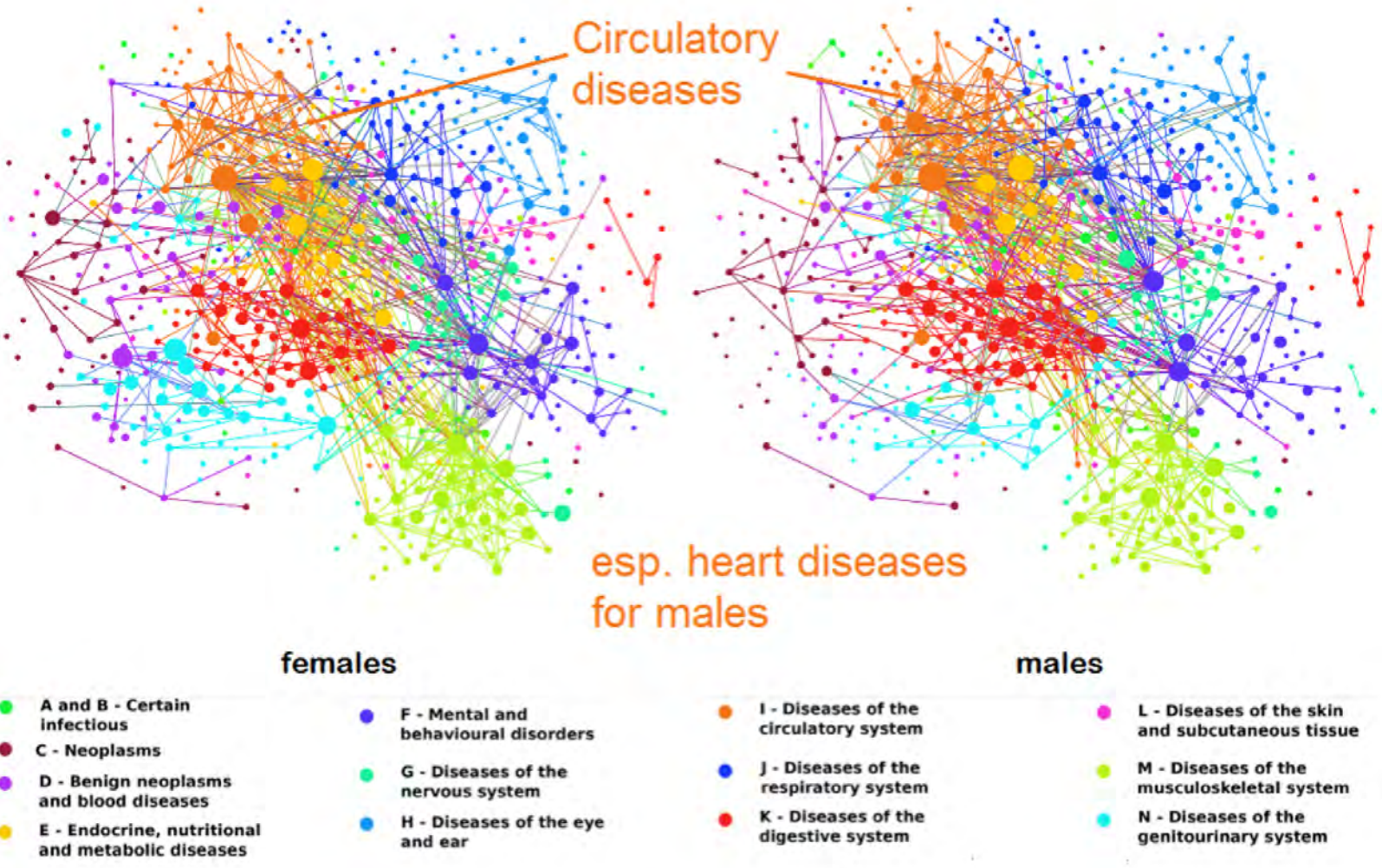

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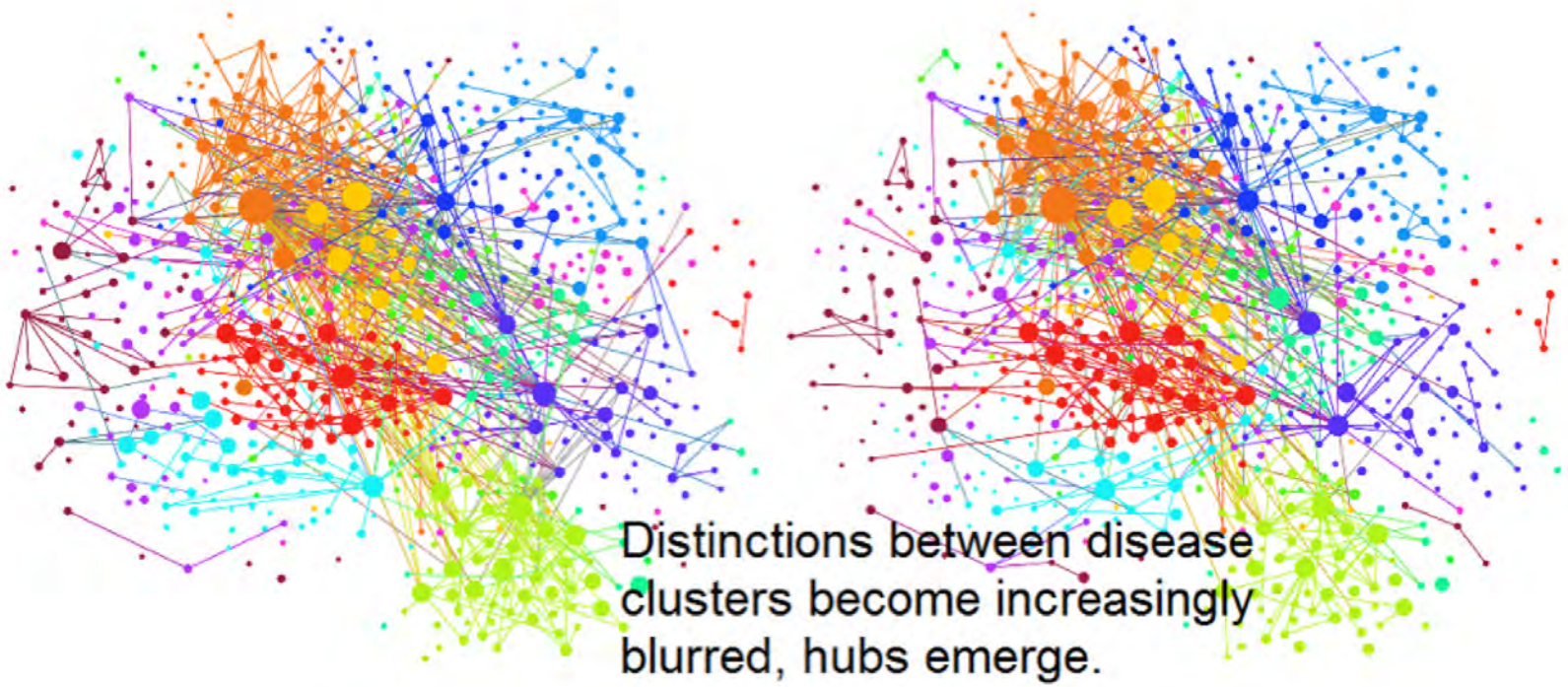

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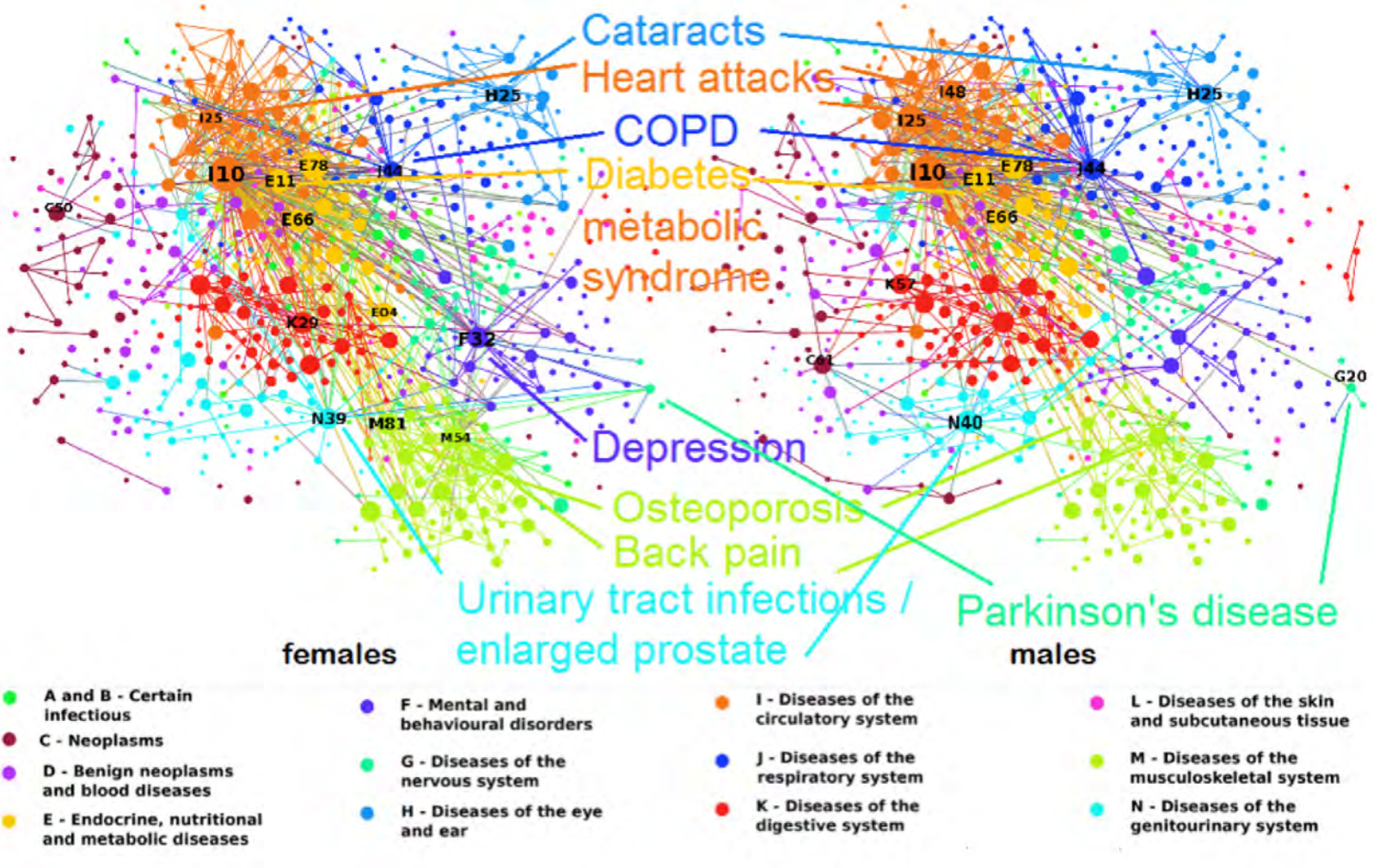

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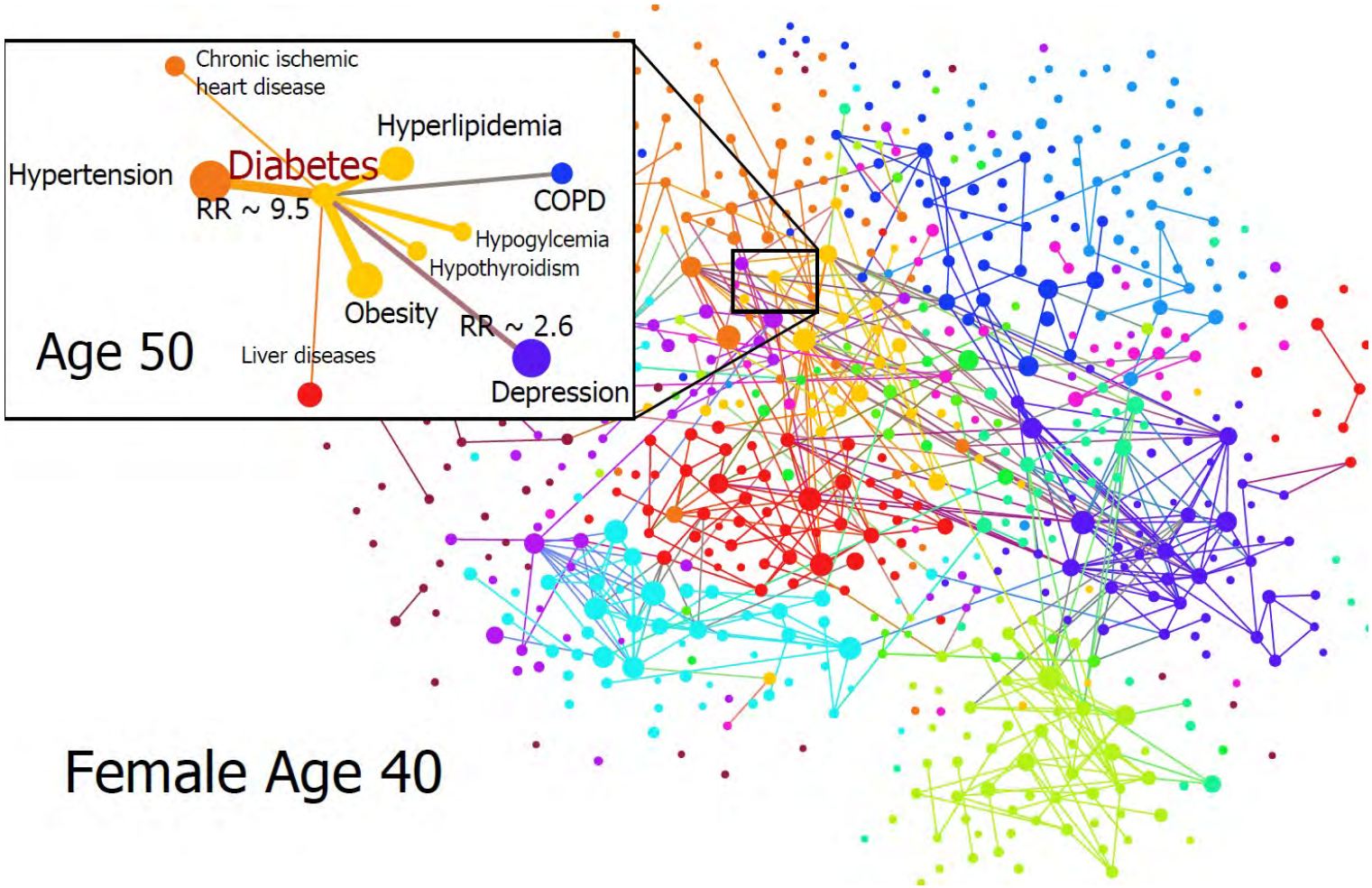
Discovery !

individual health trajectories $\rightarrow$ follow these networks

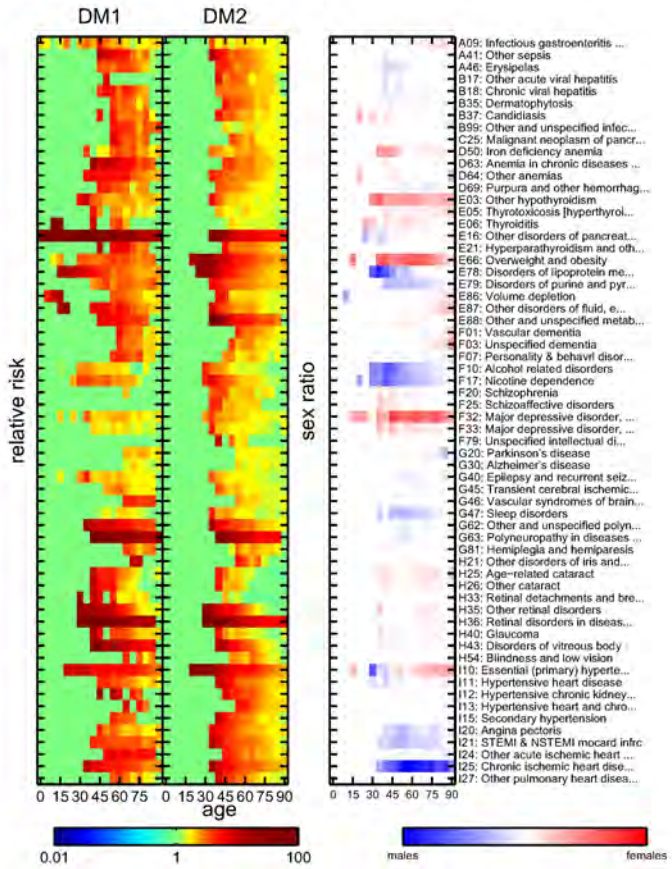
A Chmiel, P Klimek, S Thurner, New Journal of Physics 16, 115013 (2014)

predict likely disease trajectories

Individualized predictions



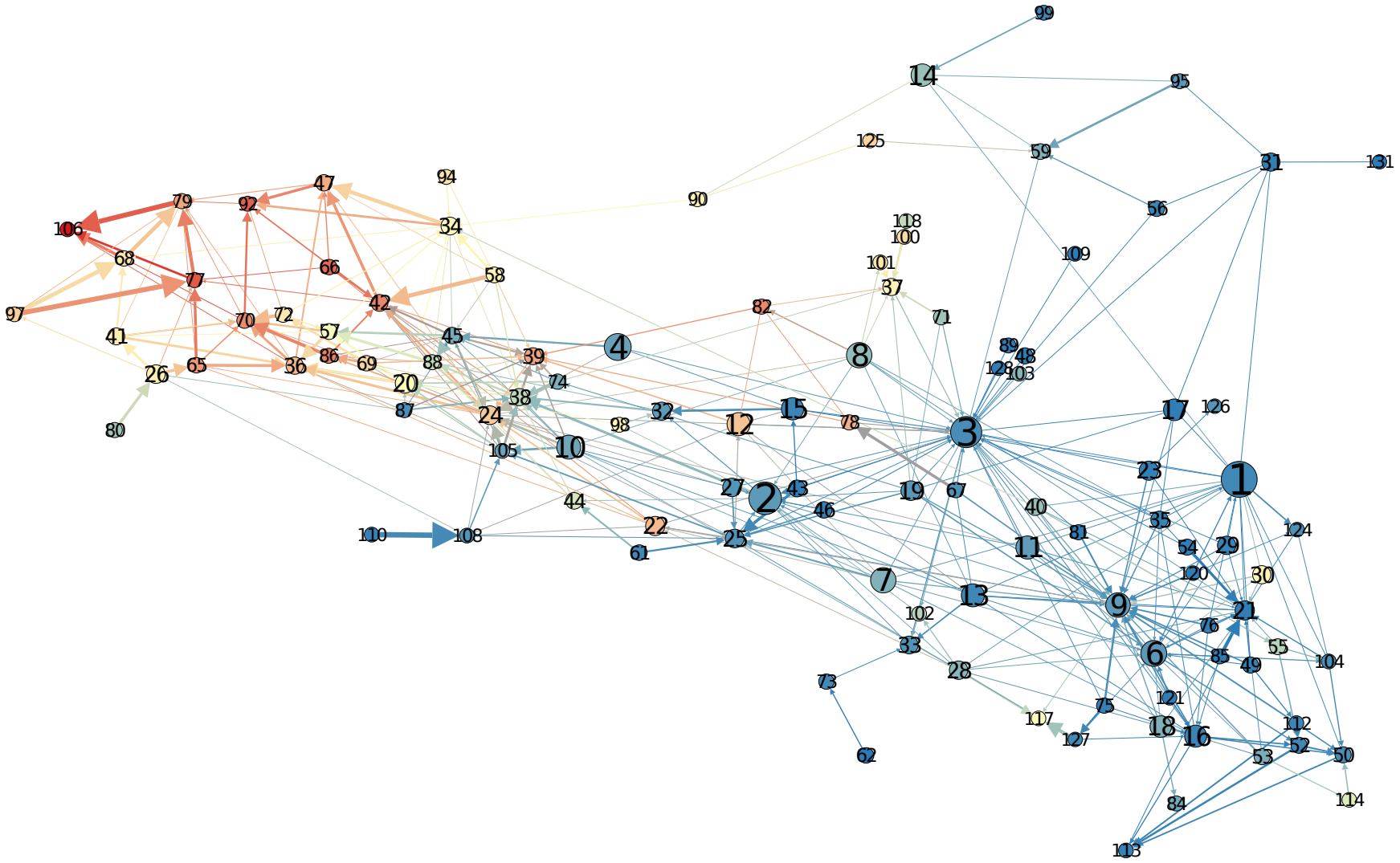
Given, you suffer diabetes: with what probability do you get other diseases?



P Klimek, A Kautzky, A Chmiel, S Thurner, PLoS Comput Biol 11, e1004125 (2015)

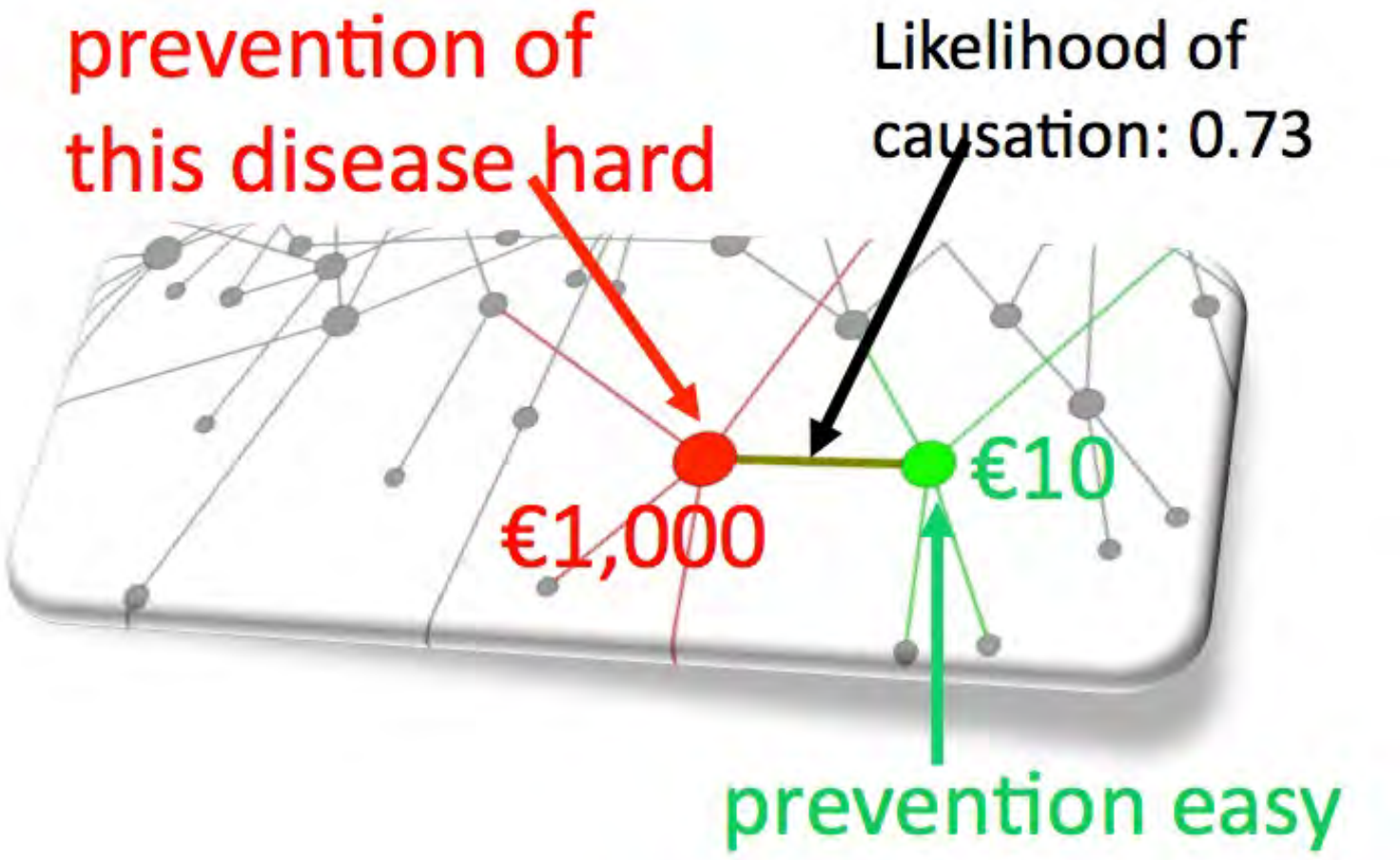
- equivalent to 40,000 epidemiological studies
- which co-morbidities are causal?
- which are significant $p < 0.00001$?
- decide controversial debates: DM $\rightarrow$ Parkinson's
- gender medicine
- **all** cases

Predicting disease trajectories



How effective is prevention?

Co-morbidity networks and prevention



Co-morbidity → check causality → fight causes

new classification of diseases?

Co-morbidity of diabetes

group 1: diabetes + A, B, C

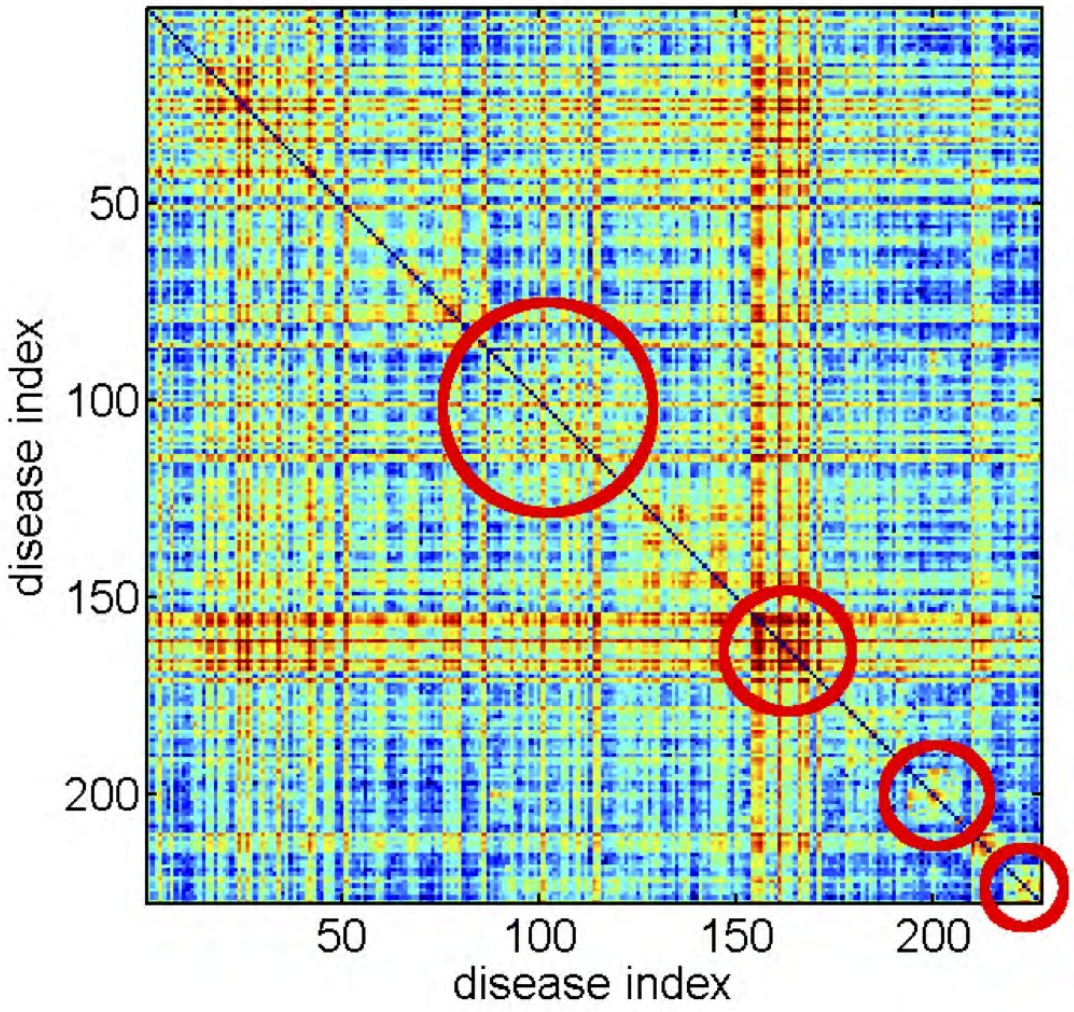
group 2: diabetes + E, F

group 3: diabetes + Y, X, Z

...

$\rightarrow$ **alternative classification of diabetes**

Co-morbidity types of diabetes



which therapy works?
which doesn't?

- group 1: therapy A
- group 2: therapy B
- compute all co-morbidities after therapy A
- berechne all co-morbidities after therapy B

$\rightarrow$ **compare:** follow up costs, hospitalization times, ...

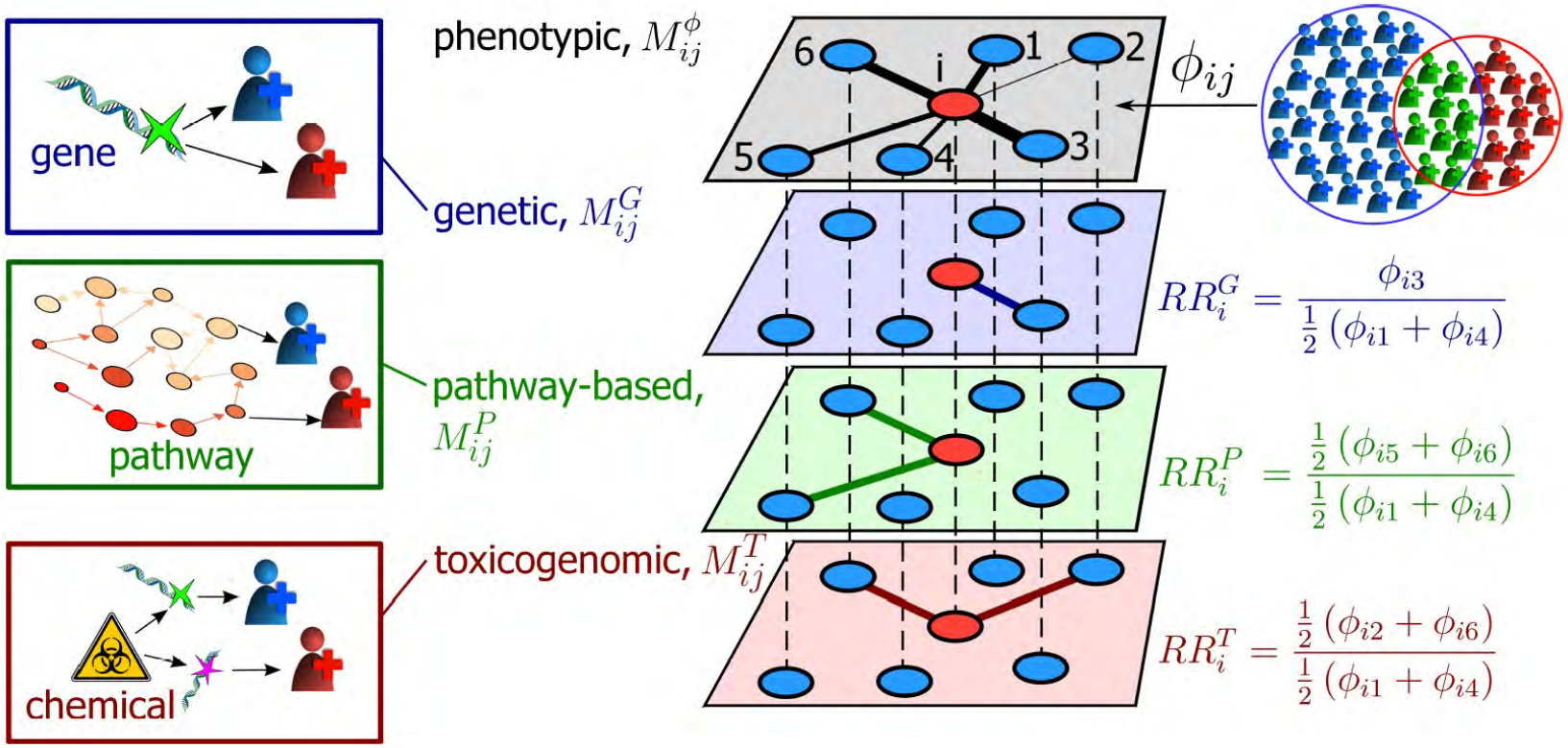
How genetic is a disease?

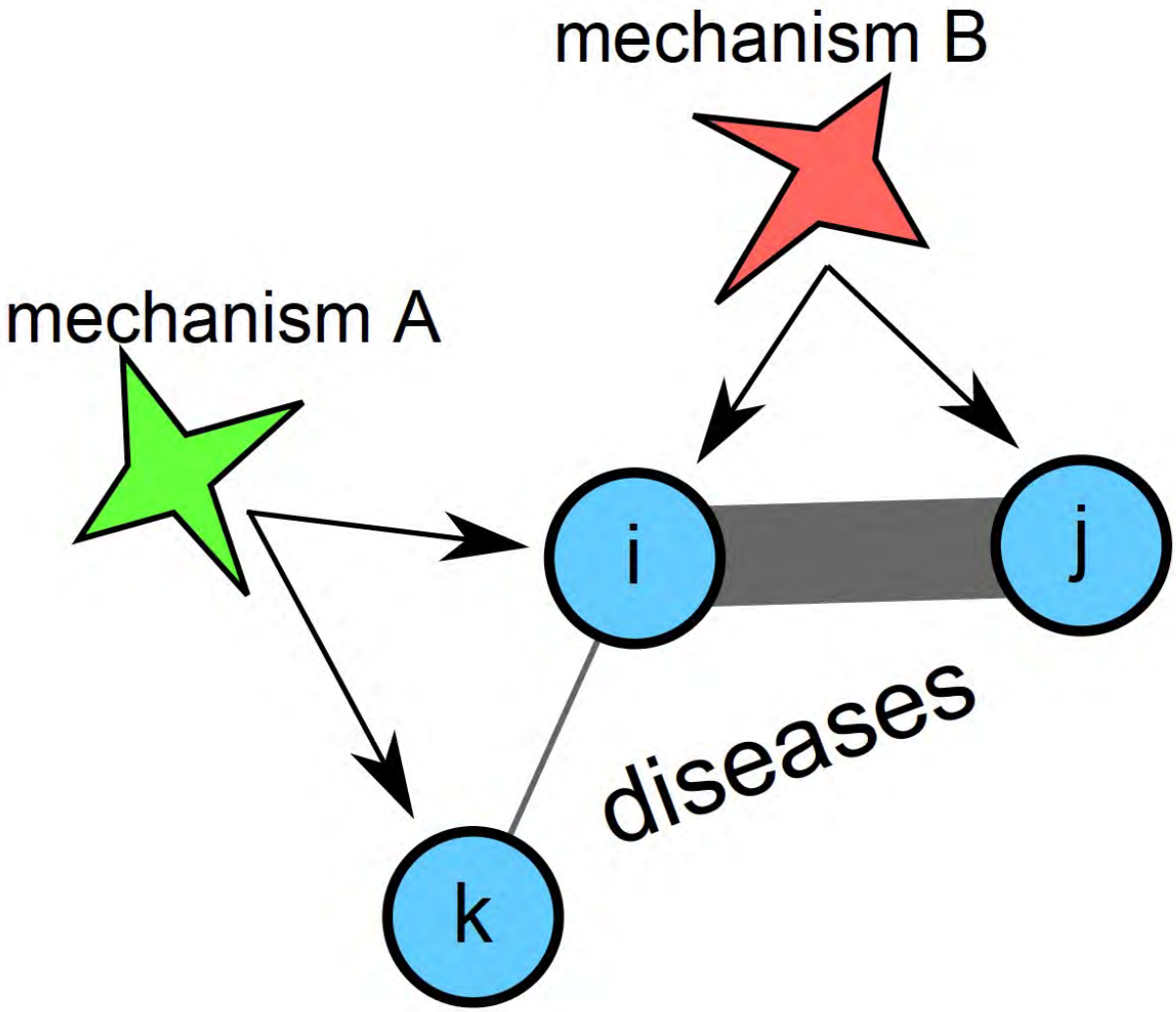
Causes of diseases

- genetic factors
- metabolic factors
- environment / toxico-genetic
- epigenetic factors

$\rightarrow$ **compare with phenotype-network**

Compare co-morbidity with genotype-network

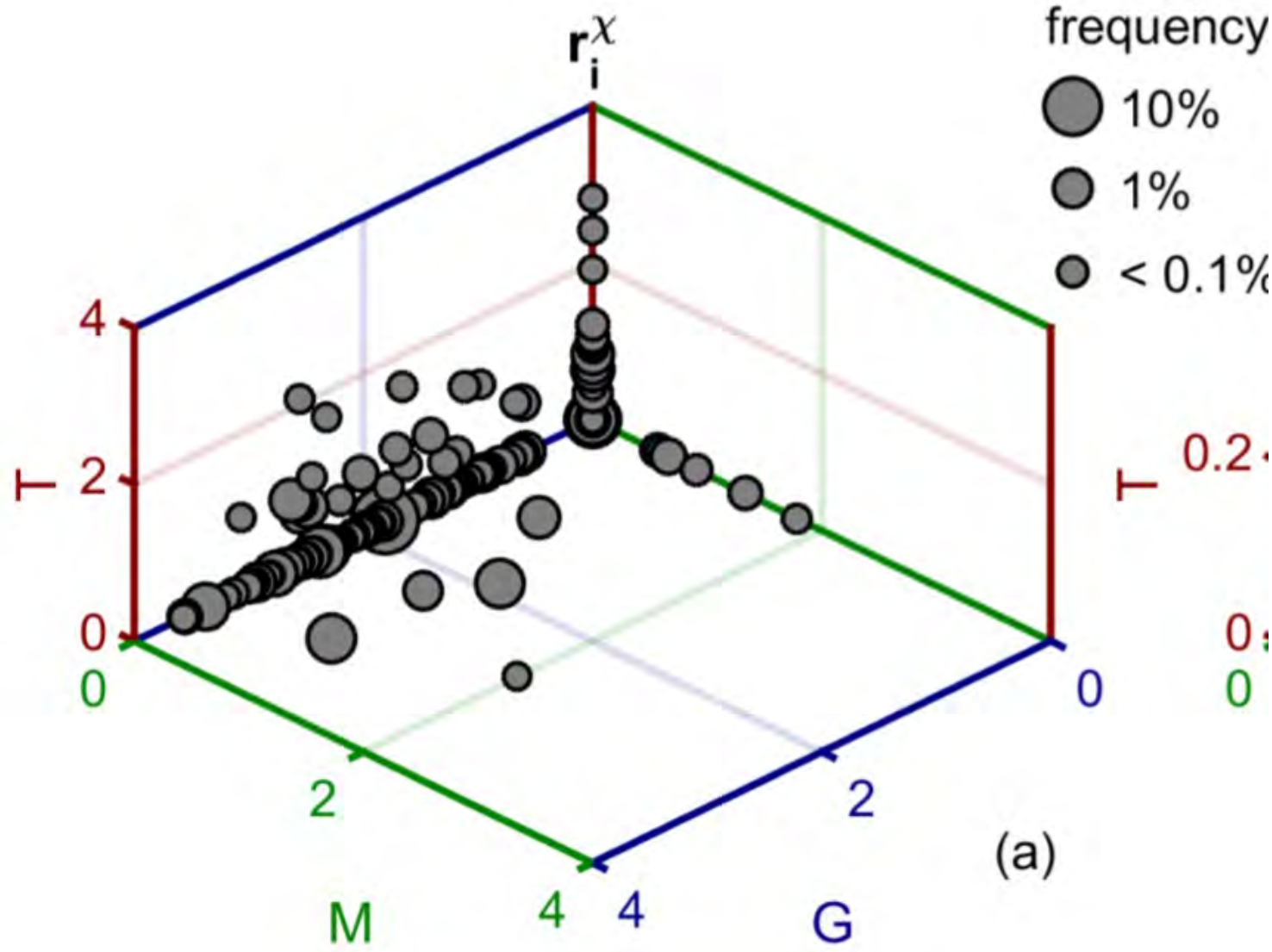



mechanism B
mechanism A
i
j
k
diseases

if co-morbidity and genotype-network are similar

$\rightarrow$ disease is genetic

Type 1 diabetes mellitus	E10	0,50
Transient cerebral ischemic attacks and related syndromes	G45	0,50
Benign neoplasm of colon, rectum, anus and anal canal	D12	0,33
Eating disorders	F50	0,33
Polycythemia vera	D45	0,25
Other diseases of intestine	K63	0,25
Other cerebrovascular diseases	I67	0,21
Other and unsp diseases of blood and blood-forming organs	D75	0,21
Other congenital malformations of heart	Q24	0,20
Malignant neoplasm of heart, mediastinum and pleura	C38	0,16
Mesothelioma	C45	0,16
Specific personality disorders	F60	0,16
Overweight and obesity	E66	0,13
Other cardiac arrhythmias	I49	0,13
Cerebral infarction	I63	0,13
Type 2 diabetes mellitus	E11	0,11
Secondary parkinsonism	G21	0,11
Other and unspecified myopathies	G72	0,11
Congenital malformations of cardiac chambers and connections	Q20	0,10
Other congenital malformations of eye	Q15	0,09
Congenital malformations of aortic and mitral valves	Q23	0,09
Parkinsons disease	G20	0,08
Primary disorders of muscles	G71	0,07
Essential (primary) hypertension	I10	0,07
Anoph	Q11	0,06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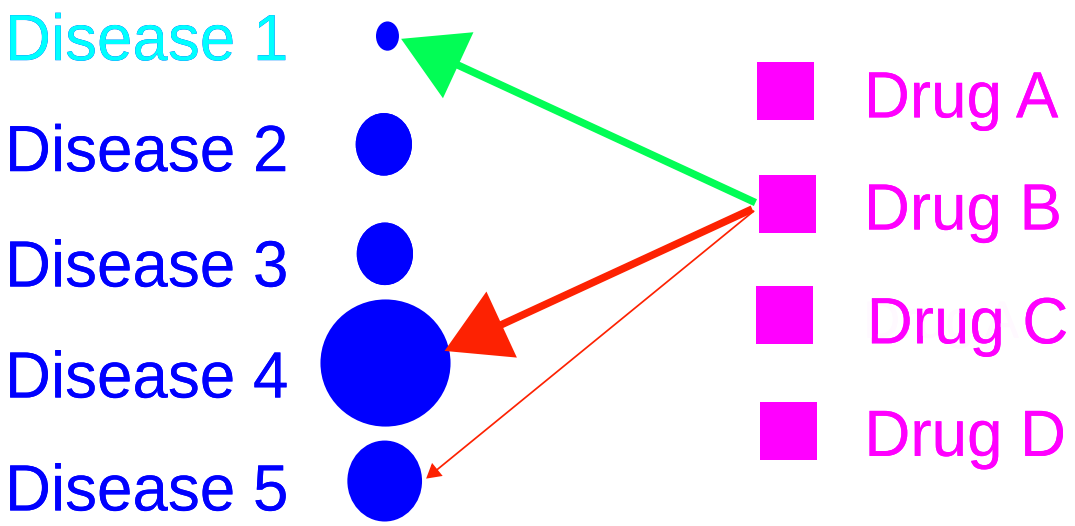
(a)

wanted side effects

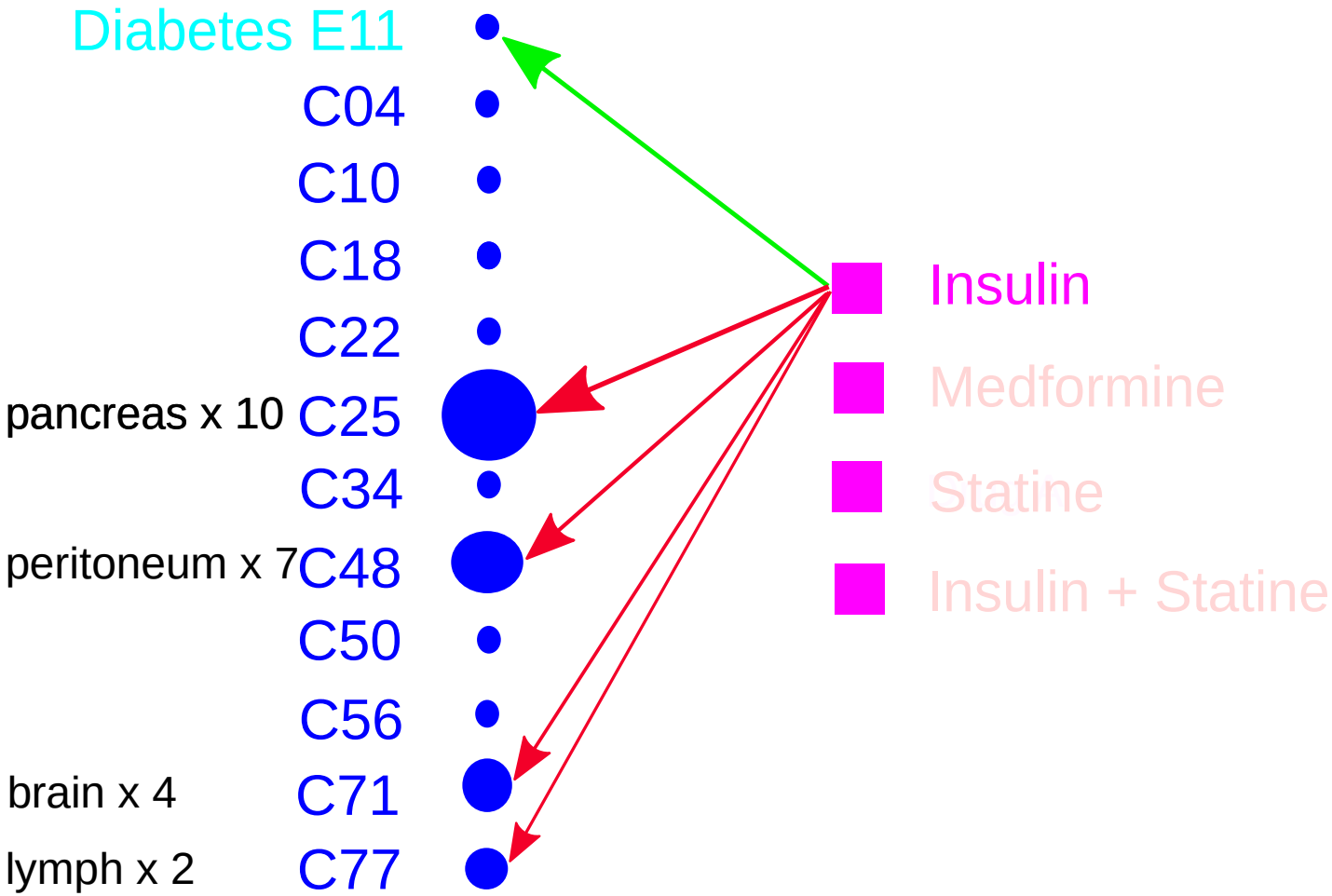
what do Austrians take?

I suffer disease 1 and get medication B

B can cause a problem 4 — side effect

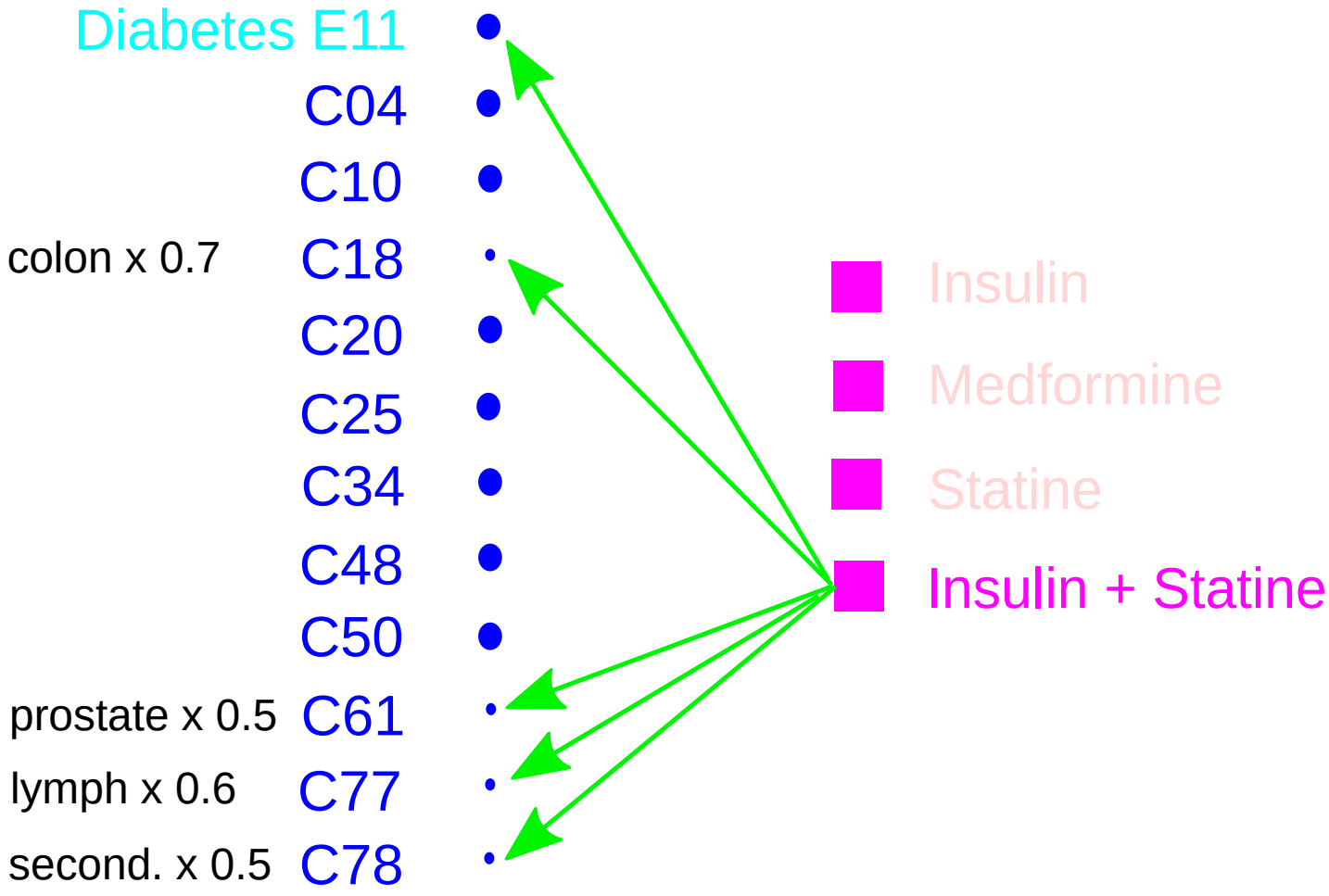


Side effects: insulin



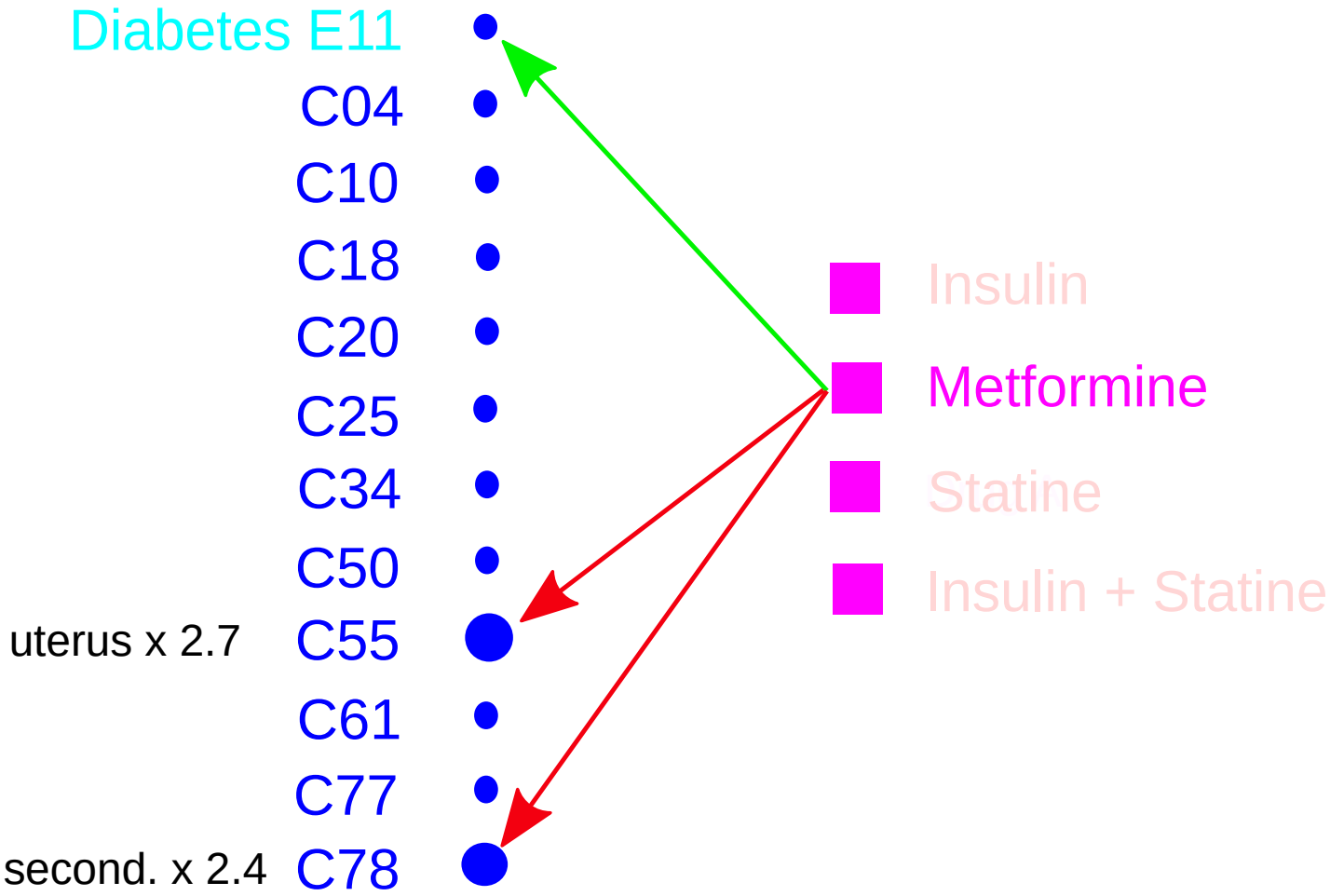
A. Kautzky-Willer, S. Thurner, and P. Klimek J Internal Medicine 281, 206-216 (2017)

Side effects: insulin+statins



A. Kautzky-Willer, S. Thurner, and P. Klimek J Internal Medicine 281, 206-216 (2017)

Side effects: metformin



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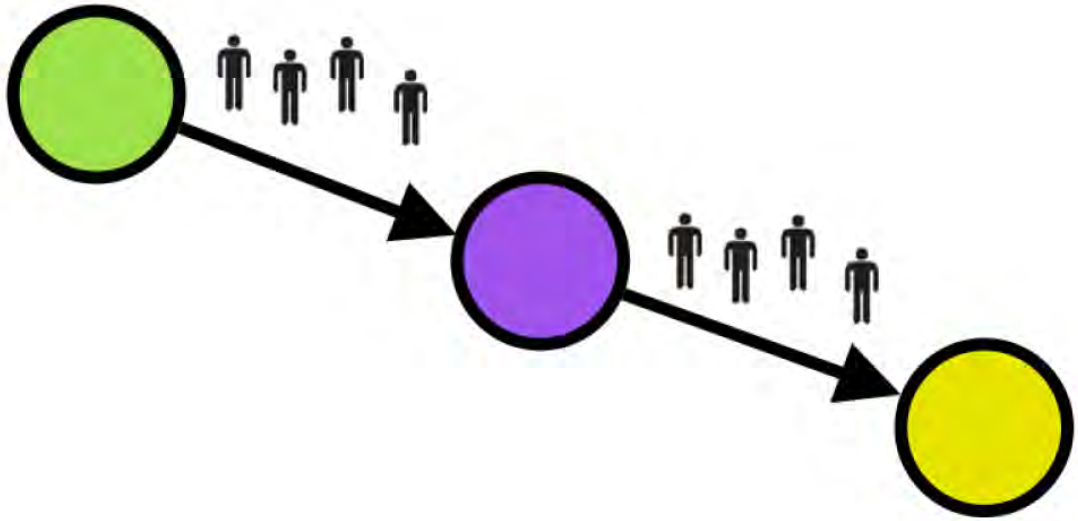
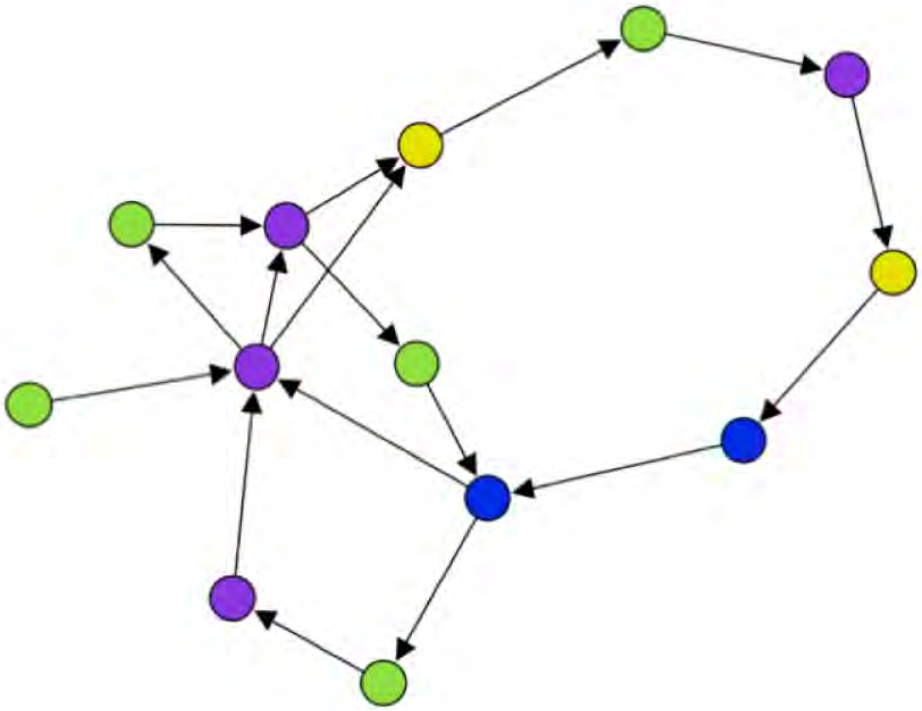
Health care system

where do Austrians get treatment?

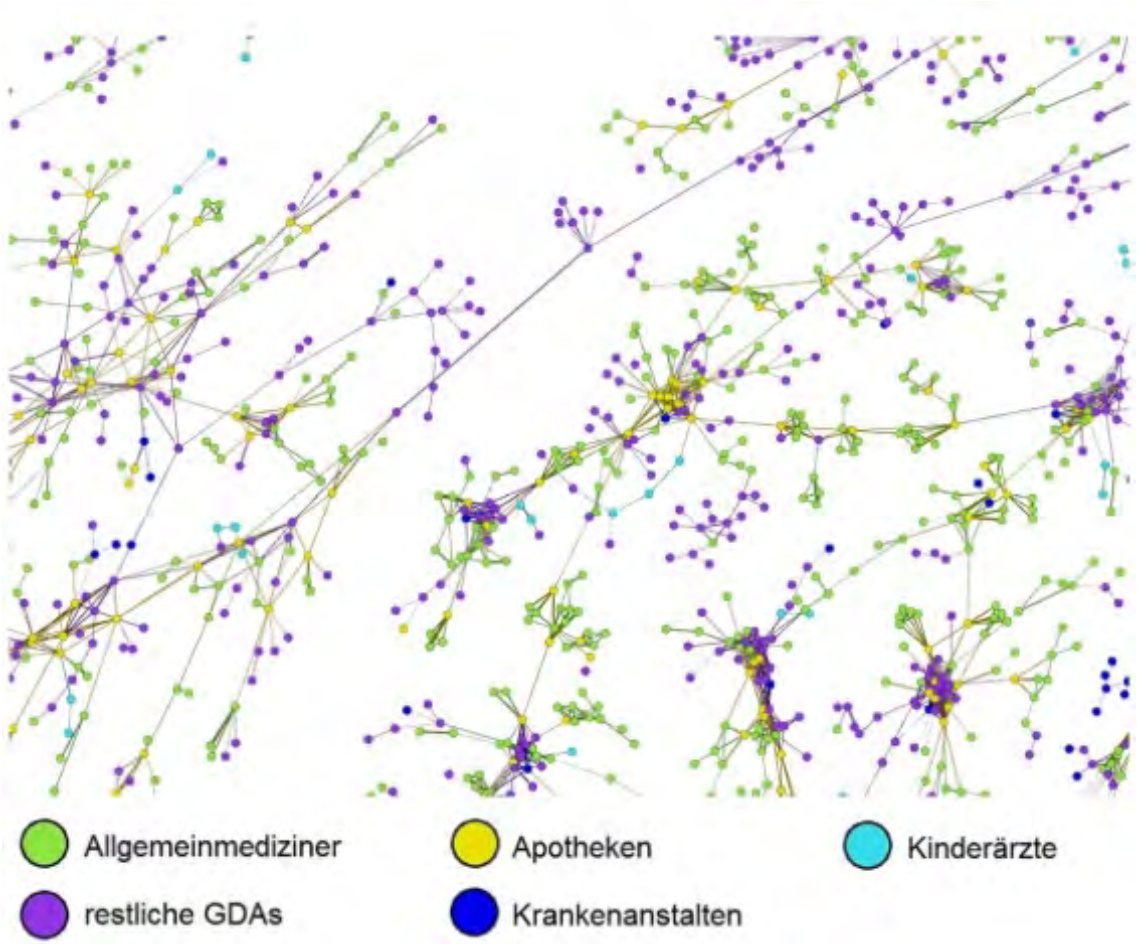


GP (doctor)
specialist
pharmacy



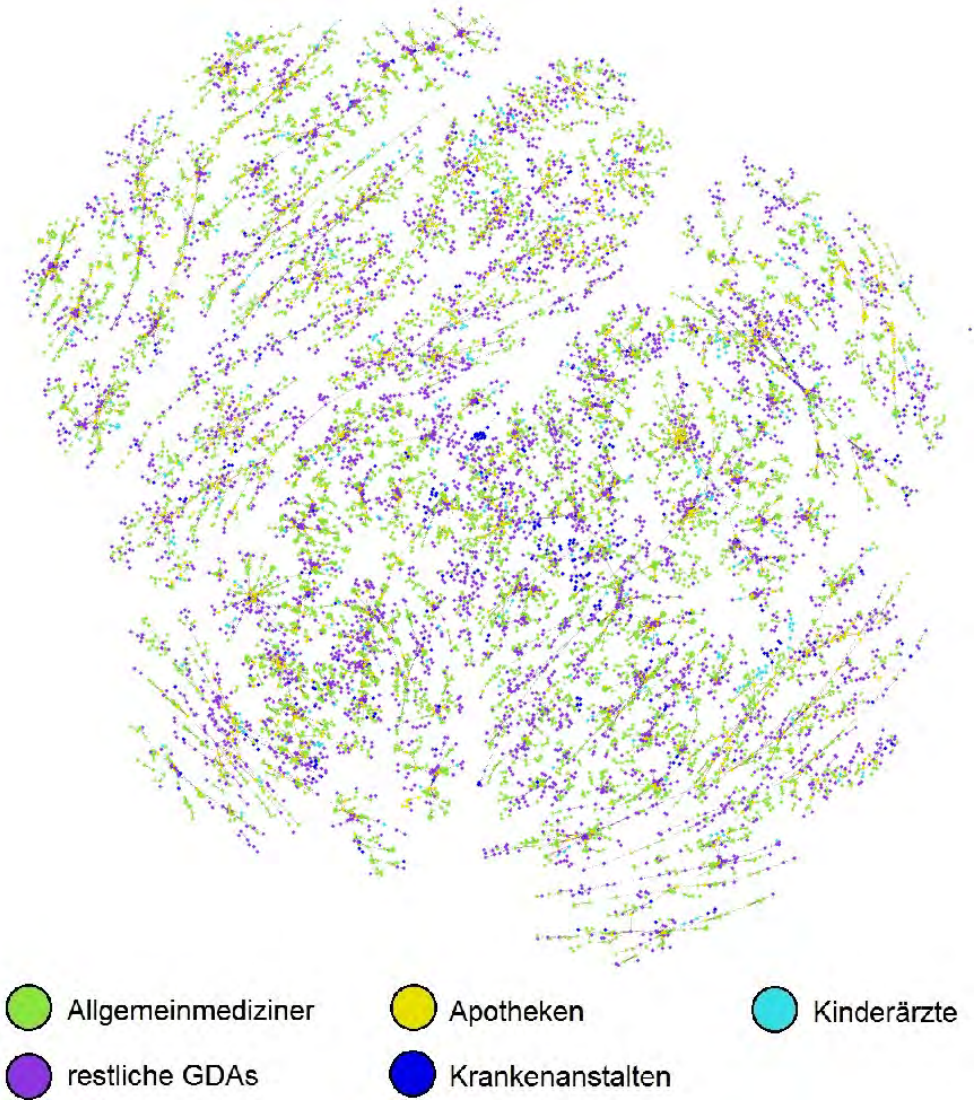
GP
specialist
pharmacy
hospital

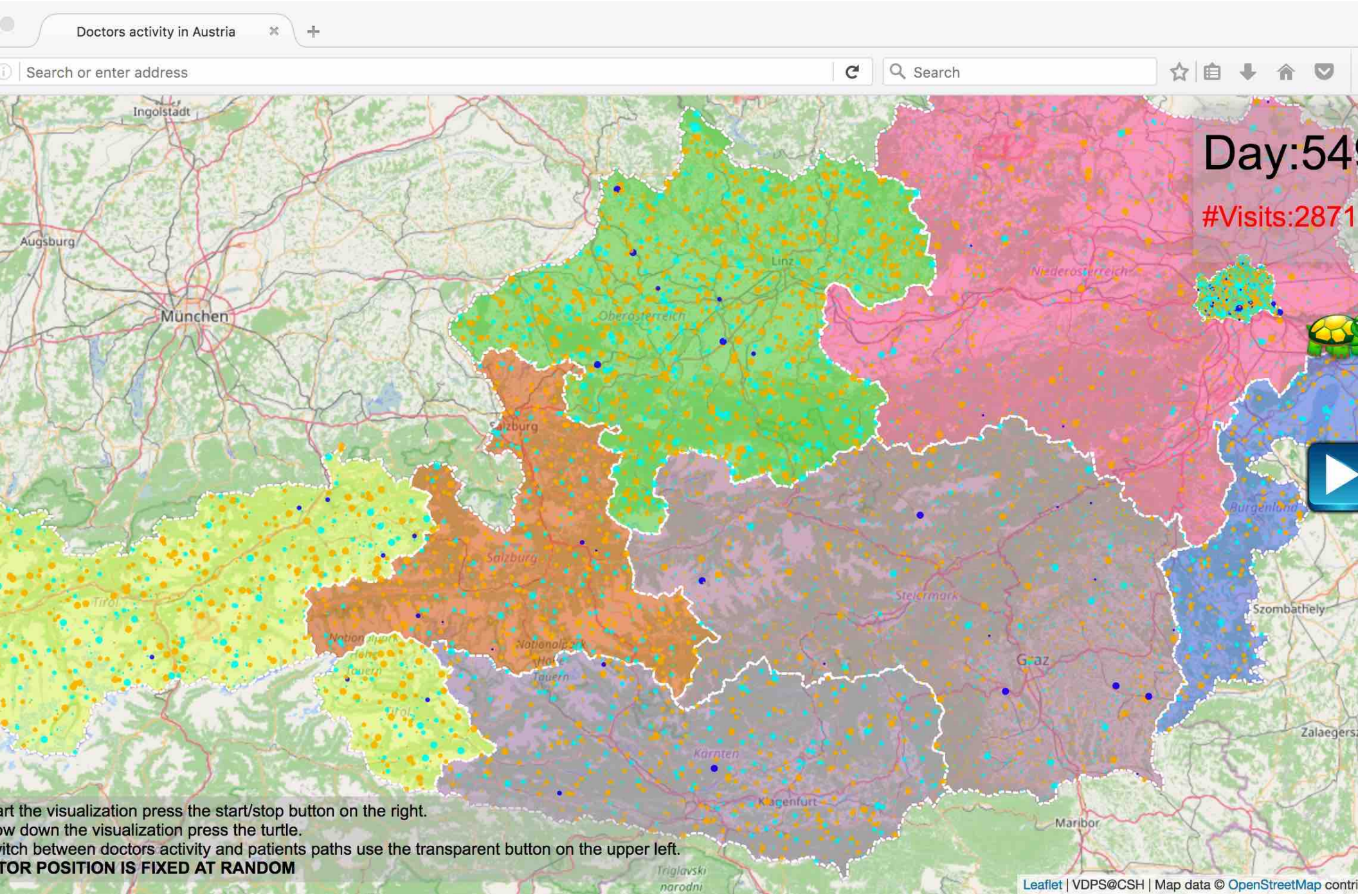
Patient flows, Austria 2006



Dorda W, et al. Analyse von Behandlungsnetzwerken (HVB, 2013)

Patient flows




Doctors activity in Austria
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Day:54
#Visits:2871
Ingolstadt
Augsburg
München
Linz
Oberösterreich
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Salzburg
Tirol
Steiermark
Burgenland
Graz
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Maribor
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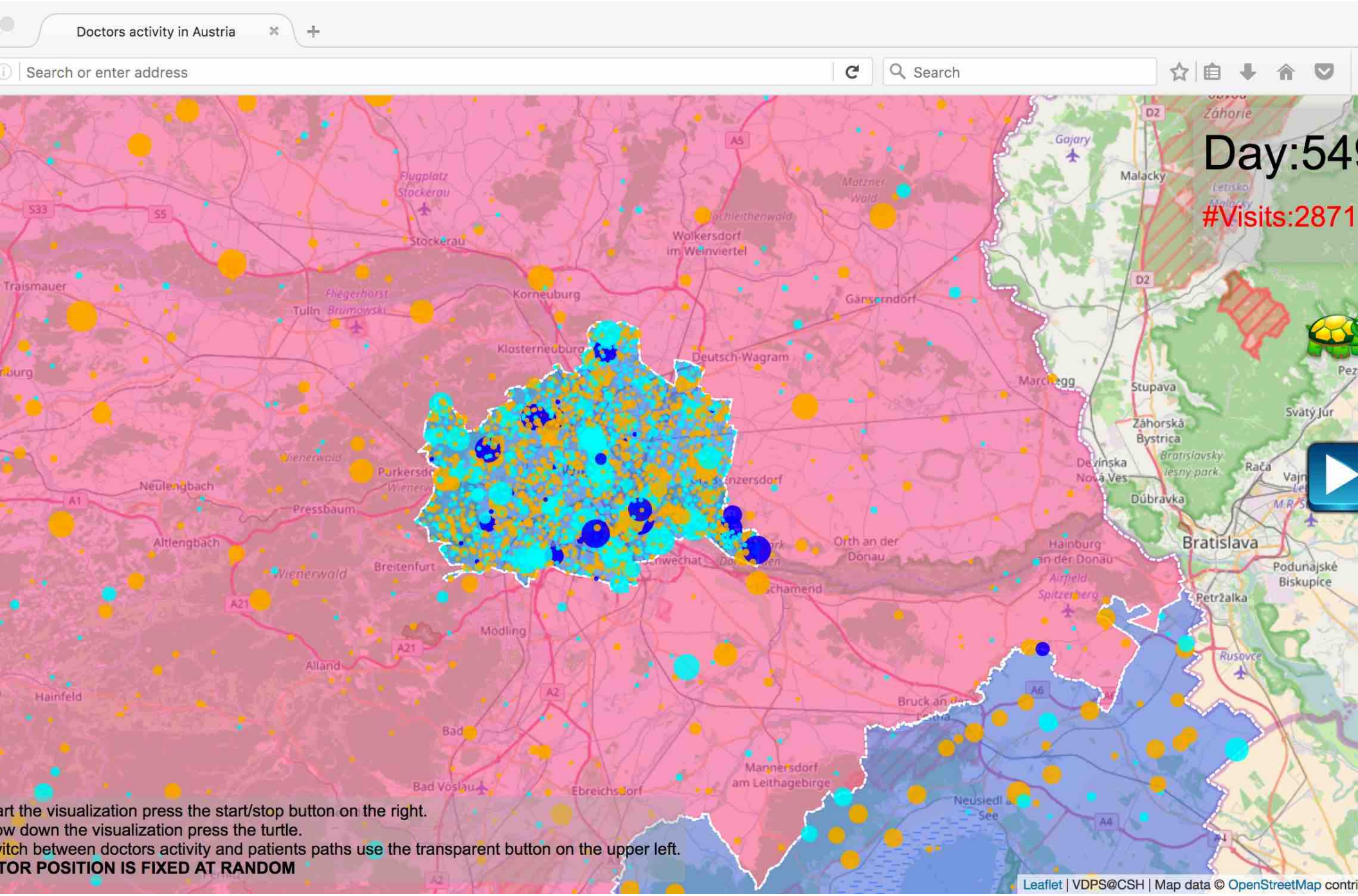
TOR POSITION IS FIXED AT RANDOM
Leaflet | VDPS@CSH | Map data © OpenStreetMap contri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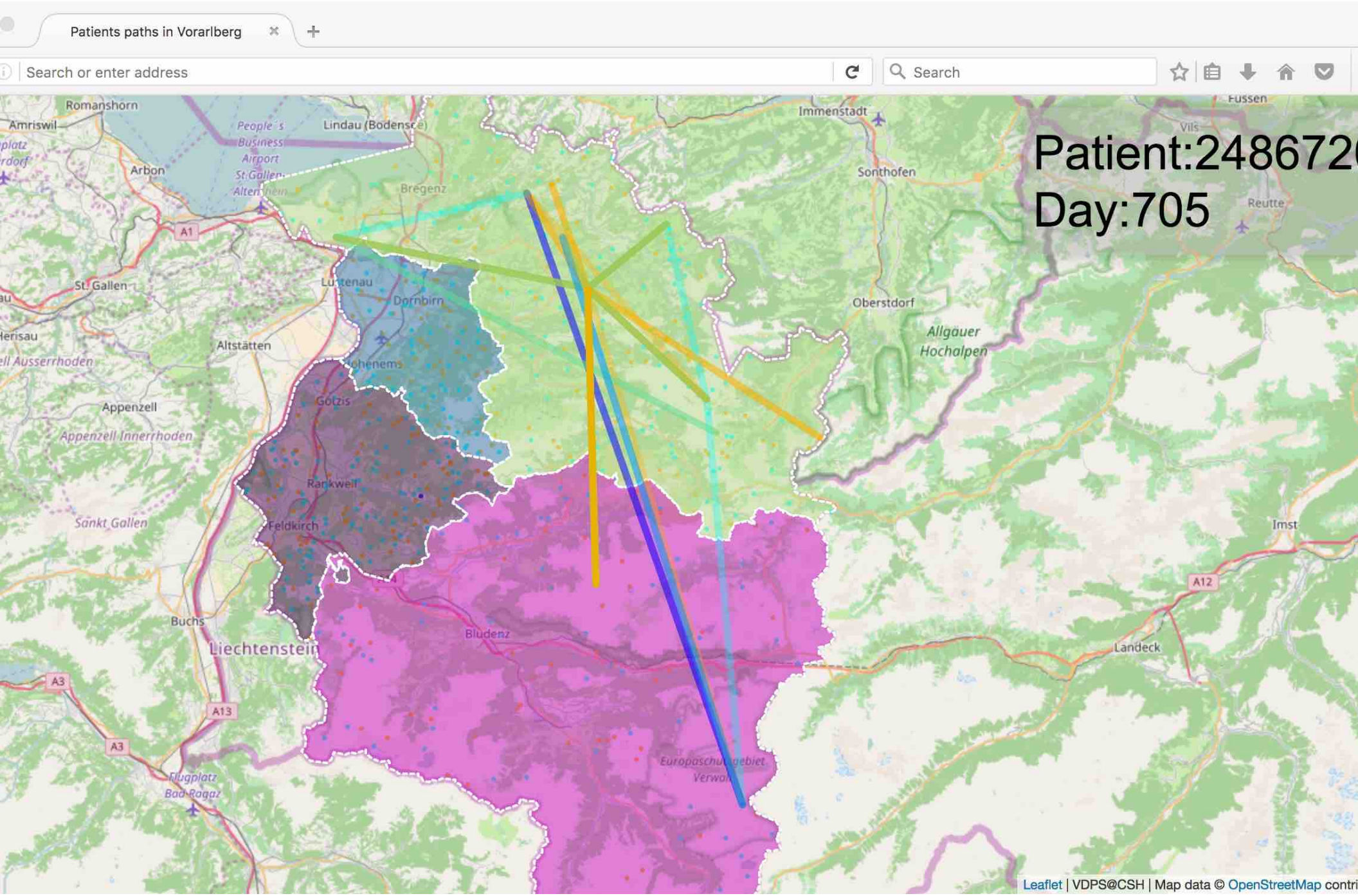
Patients paths in Vorarlberg
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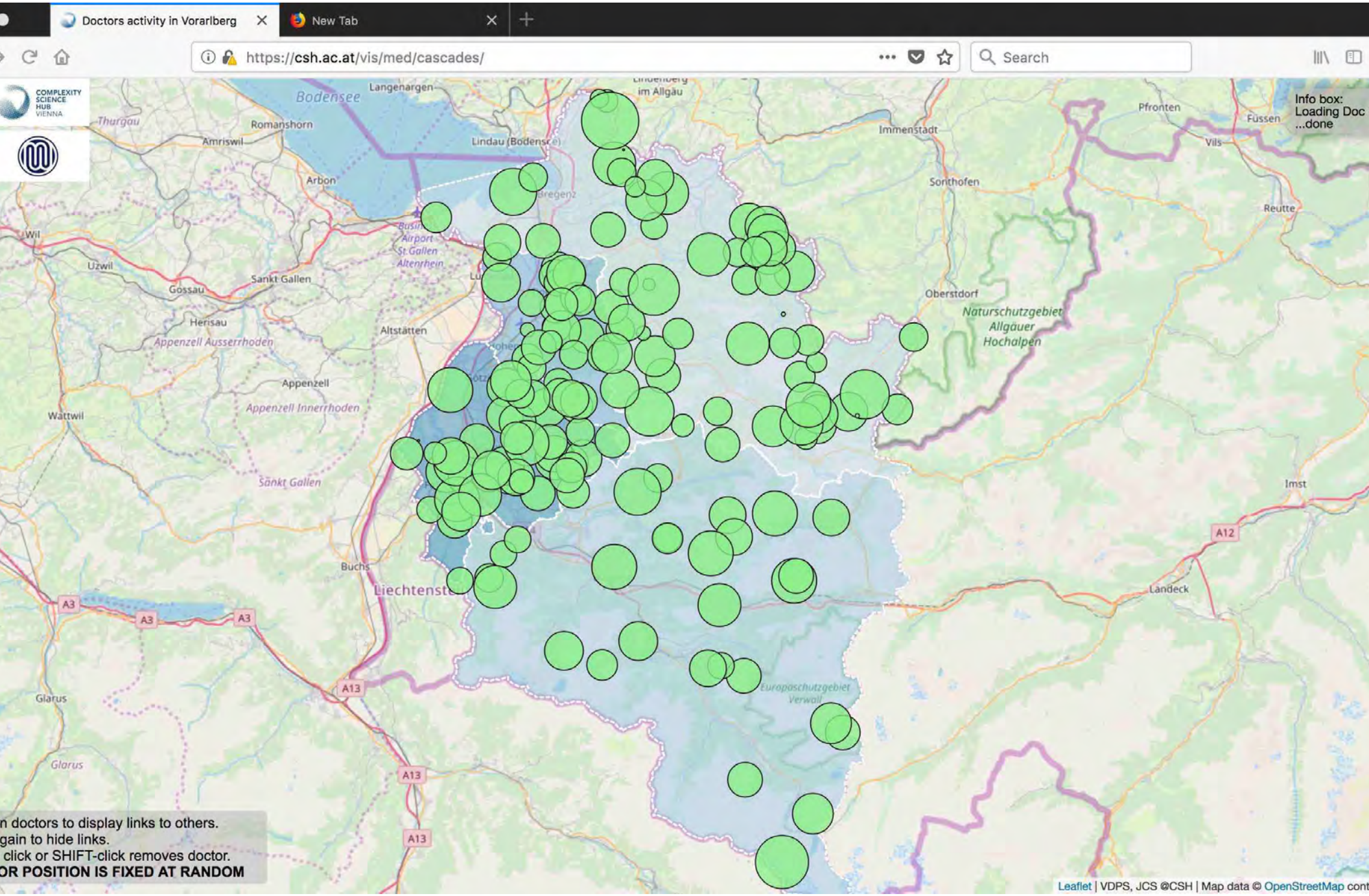
how resilient is a health care system?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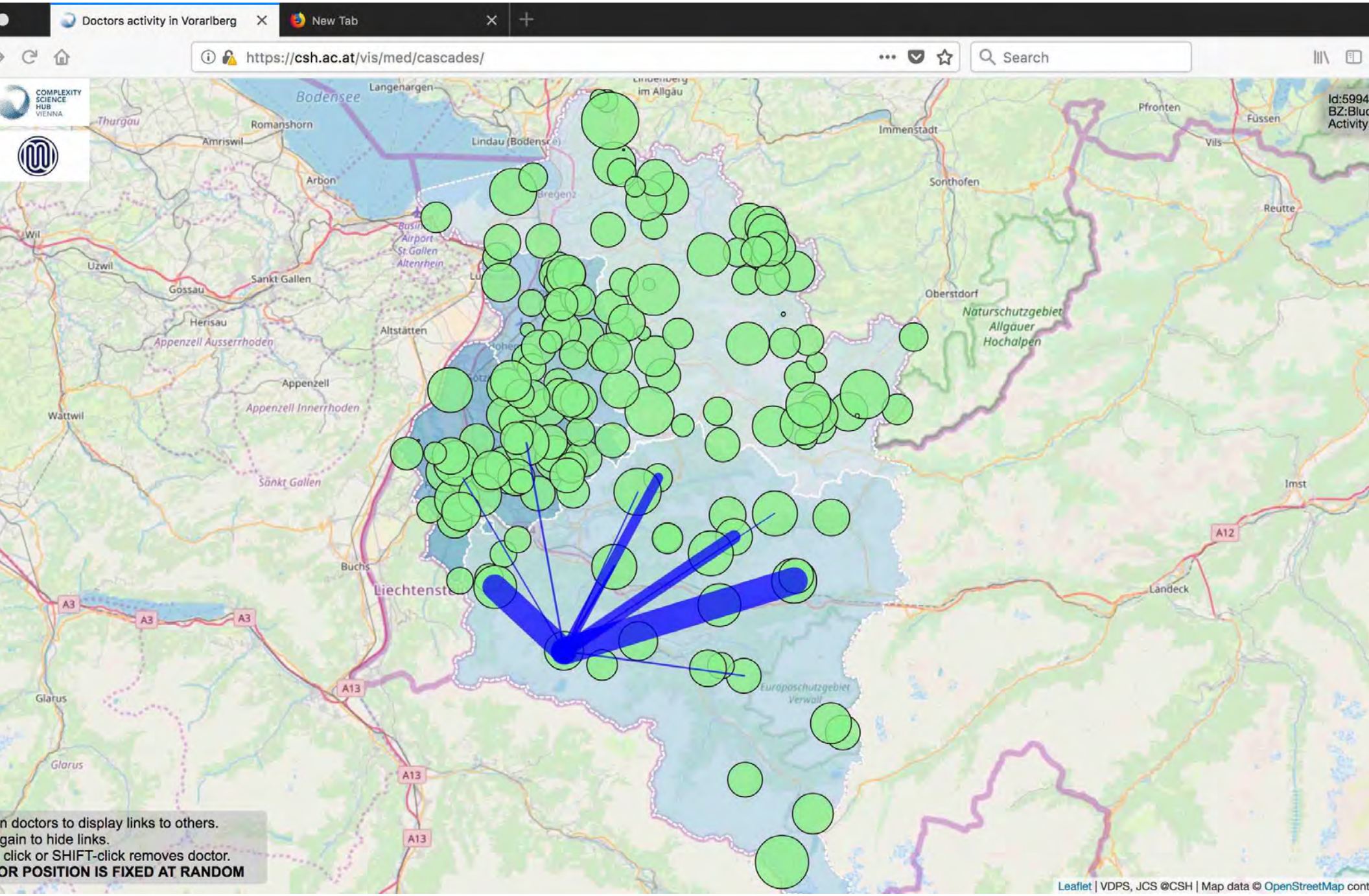
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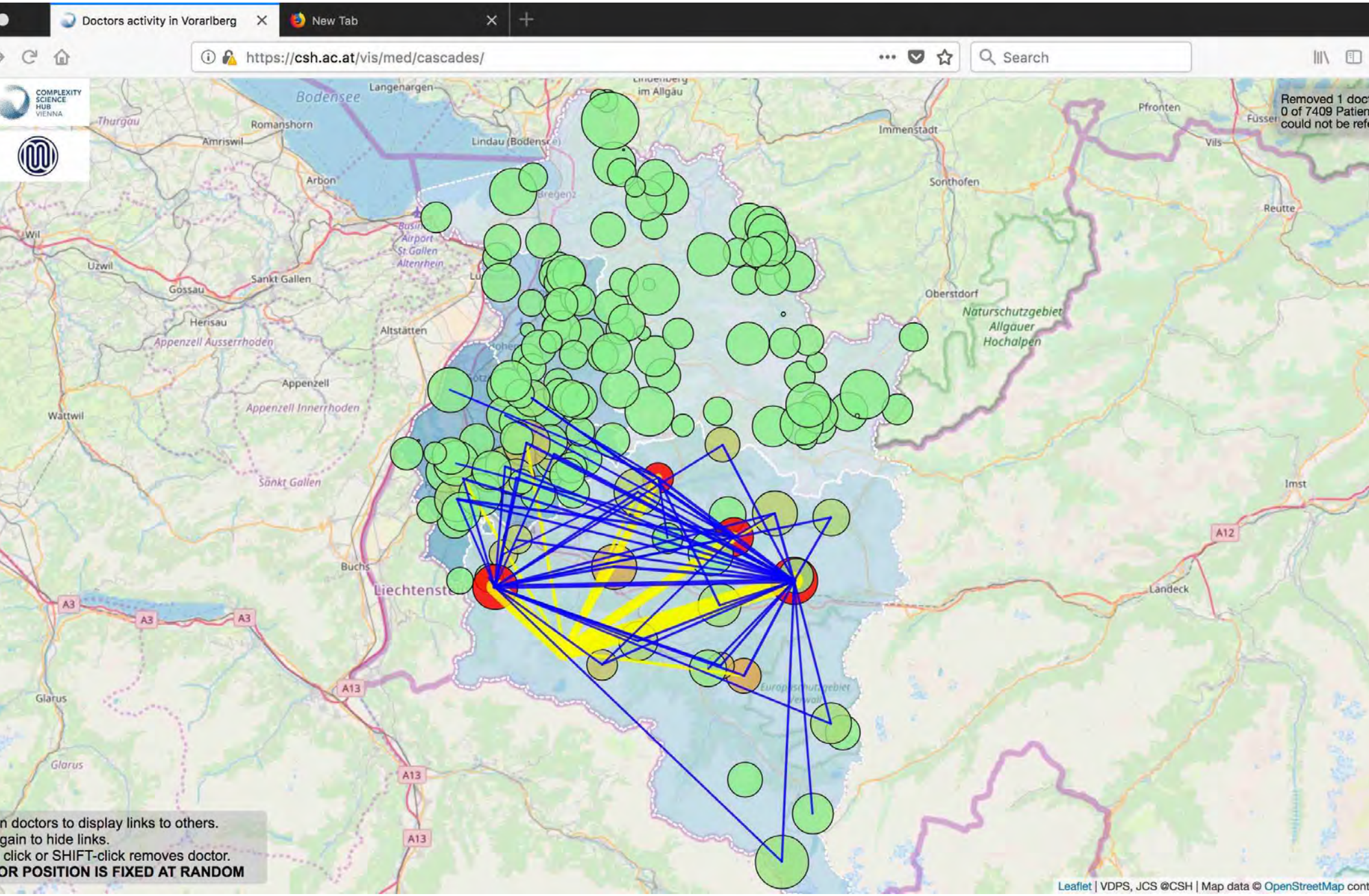
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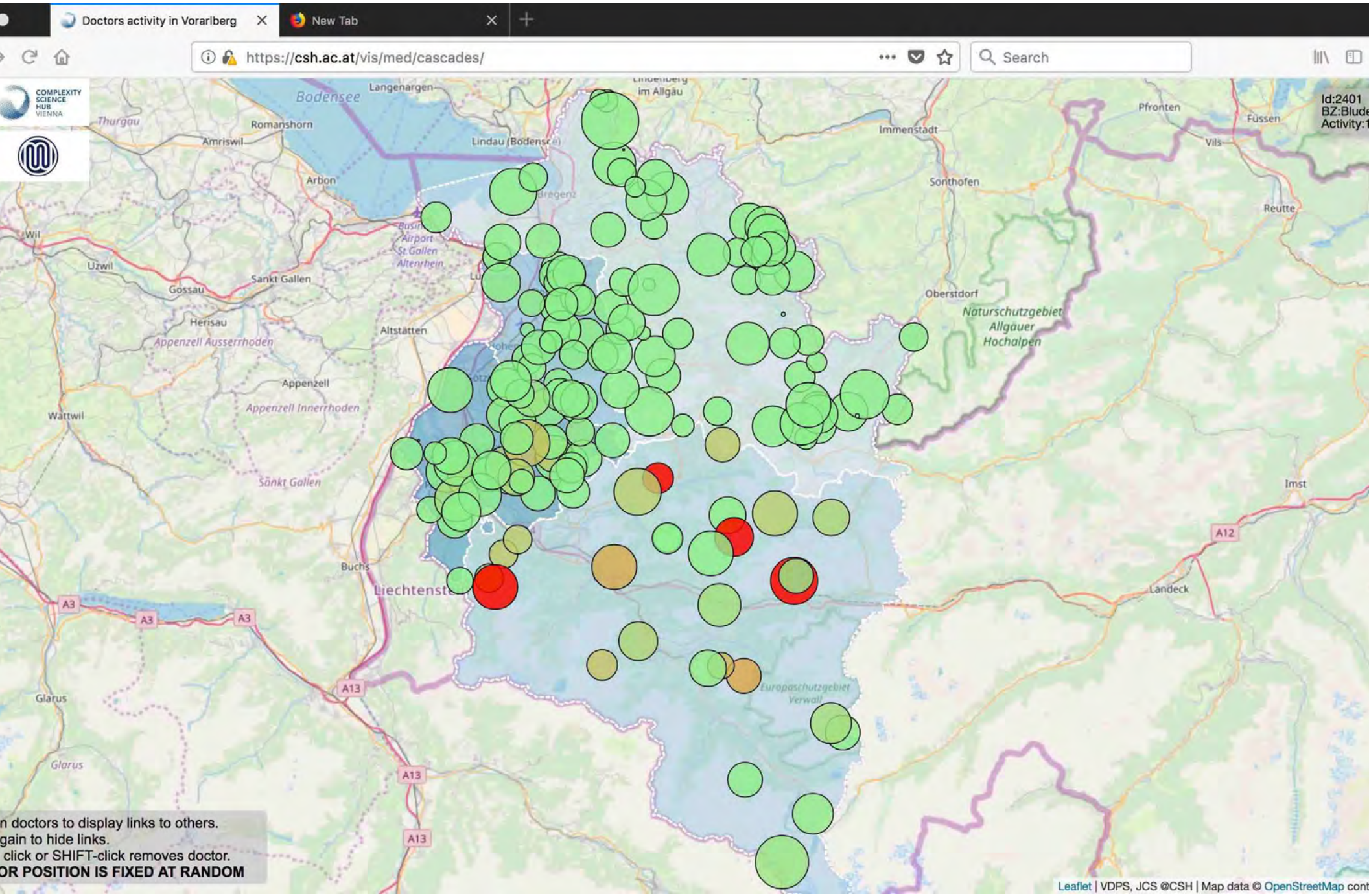
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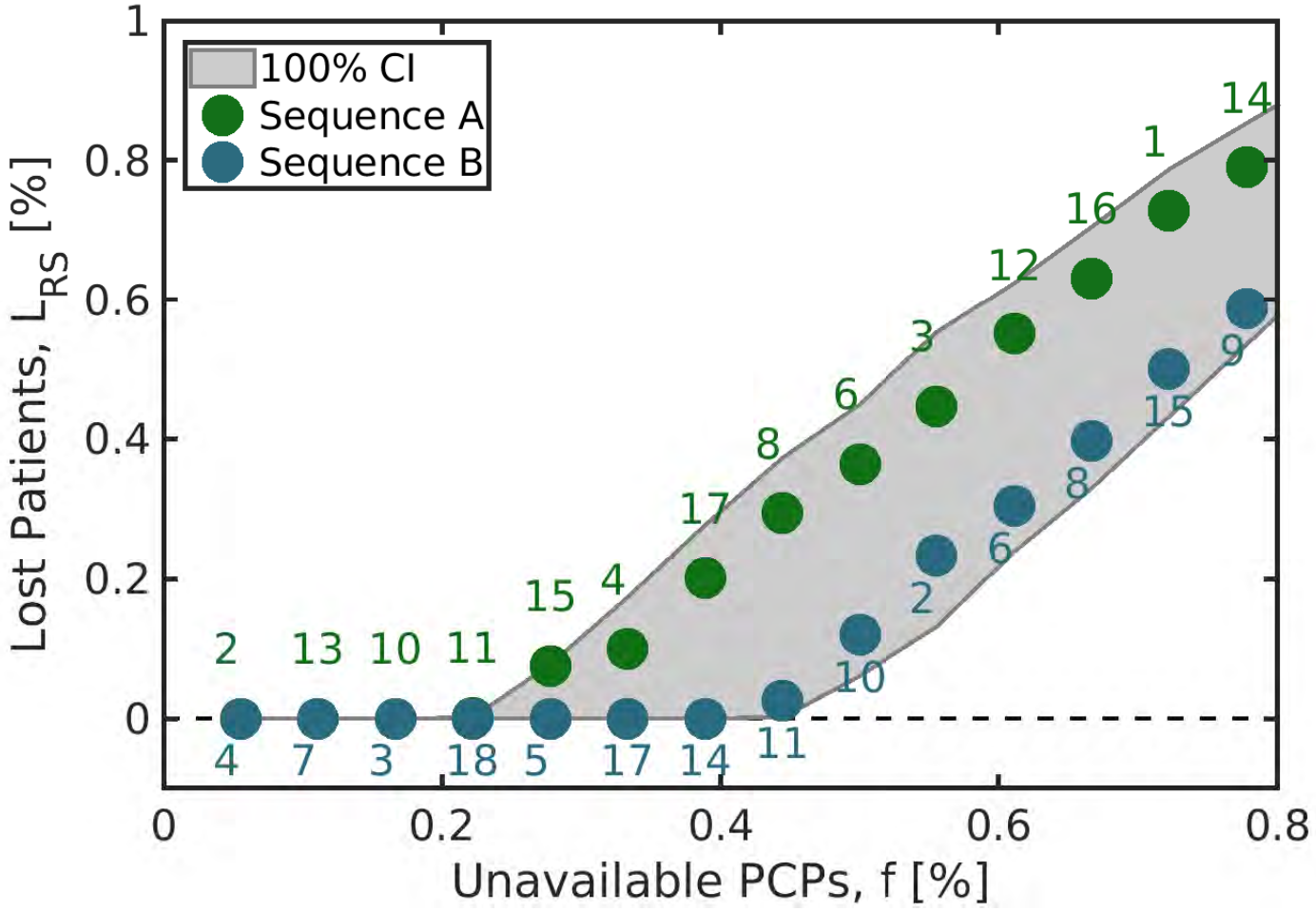
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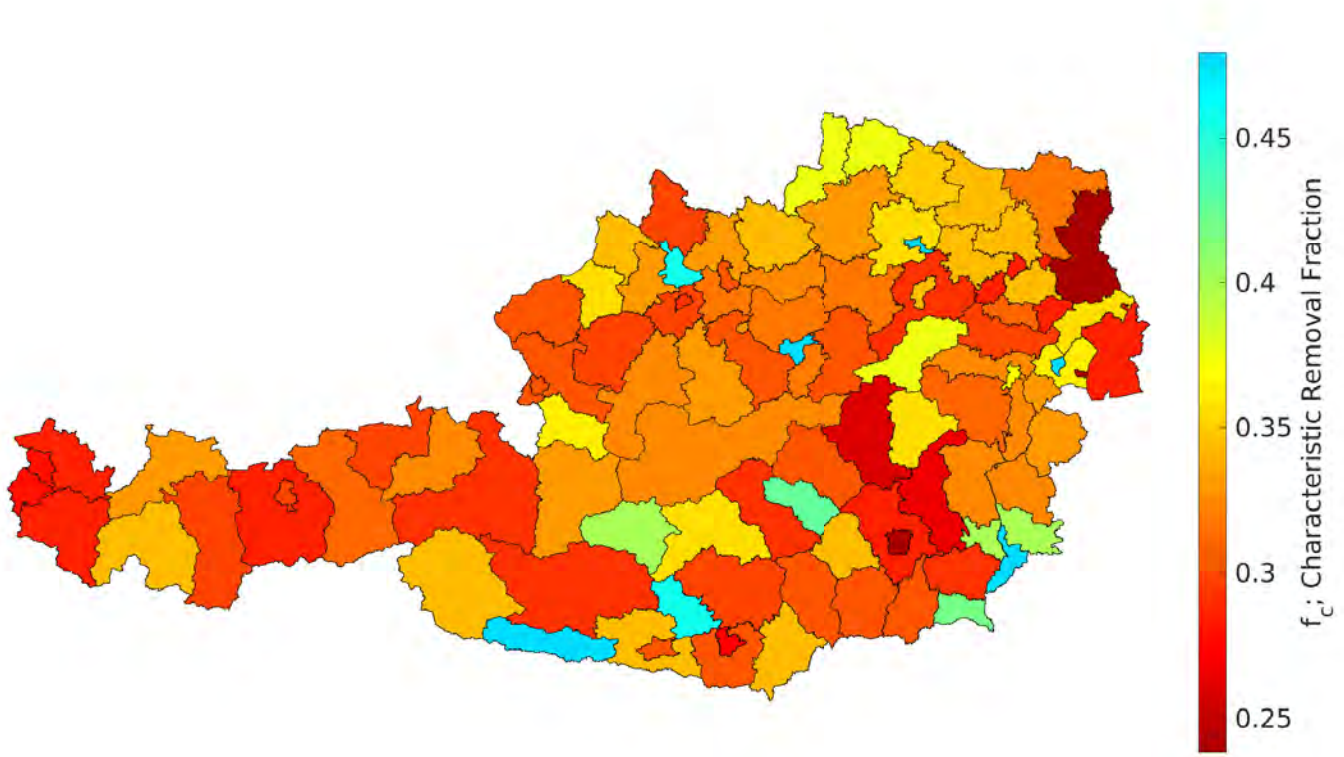
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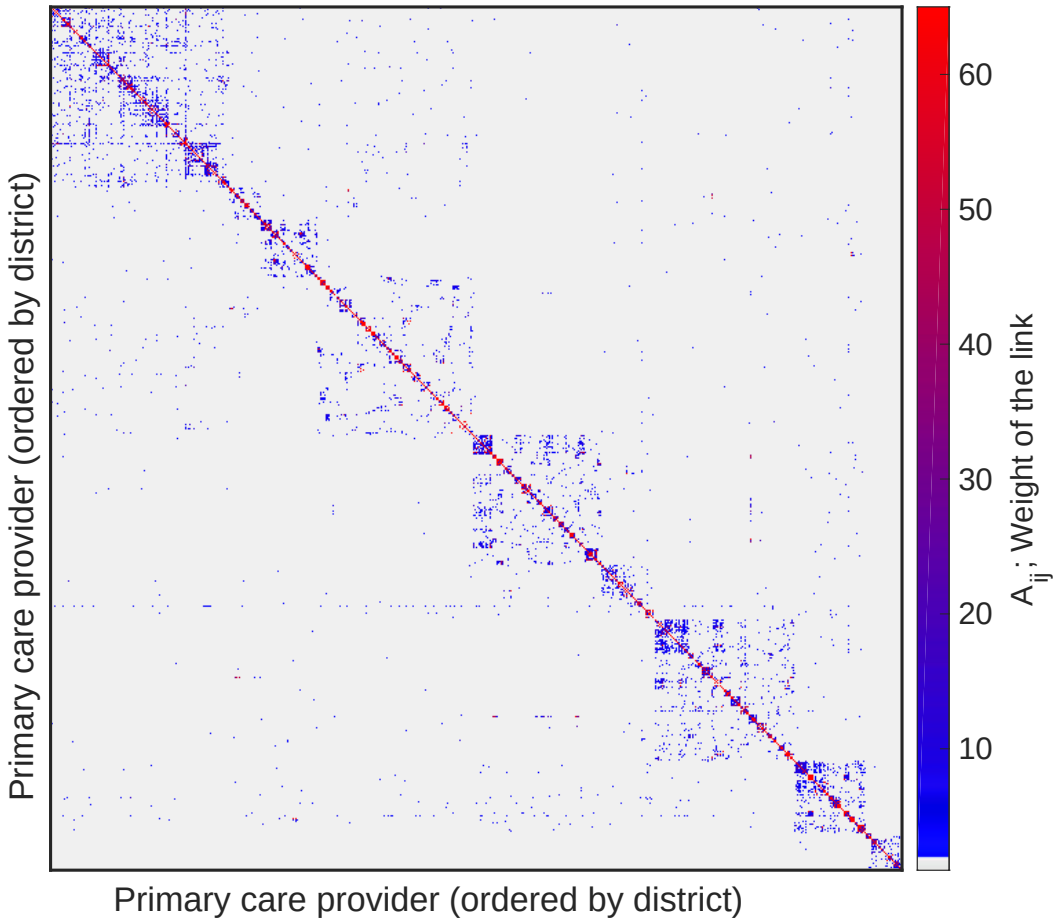
f_c; Characteristic Removal Fraction

Patient sharing network



What is the contribution?

1 what works when for whom under what conditions?

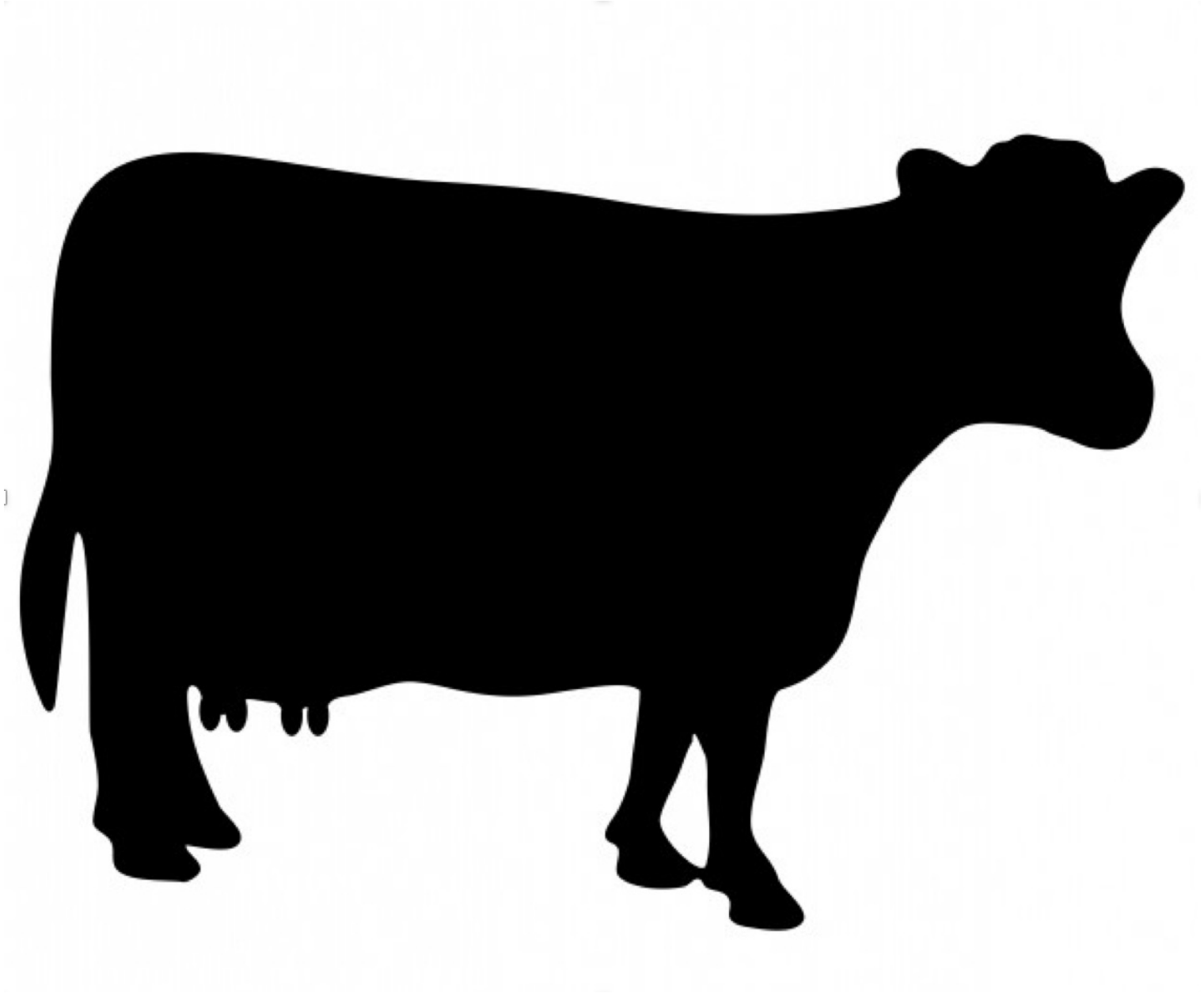
2 how efficient and resilient is the health care system?

How will medicine change?

- machines and databases will do great diagnostics
- patients will take samples and assist the diagnosis process with their data and actions
- machines will assess: what works when for whom?
- machines will offer portfolios of treatment options

medicine must interpret those and guide patients to make optimal decisions for their life

how much will we get from big data – really?



Multilayer Animal Disease Network for cows

- 2,000,000 cows
- 150,000 genomes
- farm/herd/family....
- history of food intake
- complete health care records/diagnoses/treatment/vaccines/dosage
- 80 diseases
- metabolic information
- sensor data
- tissue samples

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