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Methodological Novelties and Causal Inference in Epidemiology

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Rationale and Content of the Talk

- Focus:
  - advancements in medicine towards data-intensive approaches (molecular epidemiology).
- Novelties:
  - causal inference?
- My take:

  the data-intensive nature of causal inference in molecular epidemiology is an incremental – not particularly novel – change for the field.

Outline of the Talk

1. Presentation of the case-study: molecular epidemiology and its data-intensive features.
2. Epistemologically interesting aspects.
3. Causal inference: a novelty for epidemiology?

1. Molecular Epidemiology as Data-Intensive Science

What is Molecular Epidemiology?

> "The study of the distribution and determinants of disease and other health states in human populations by means of group comparisons for the purpose of improving population health"
>
> — Broadbent (2013)

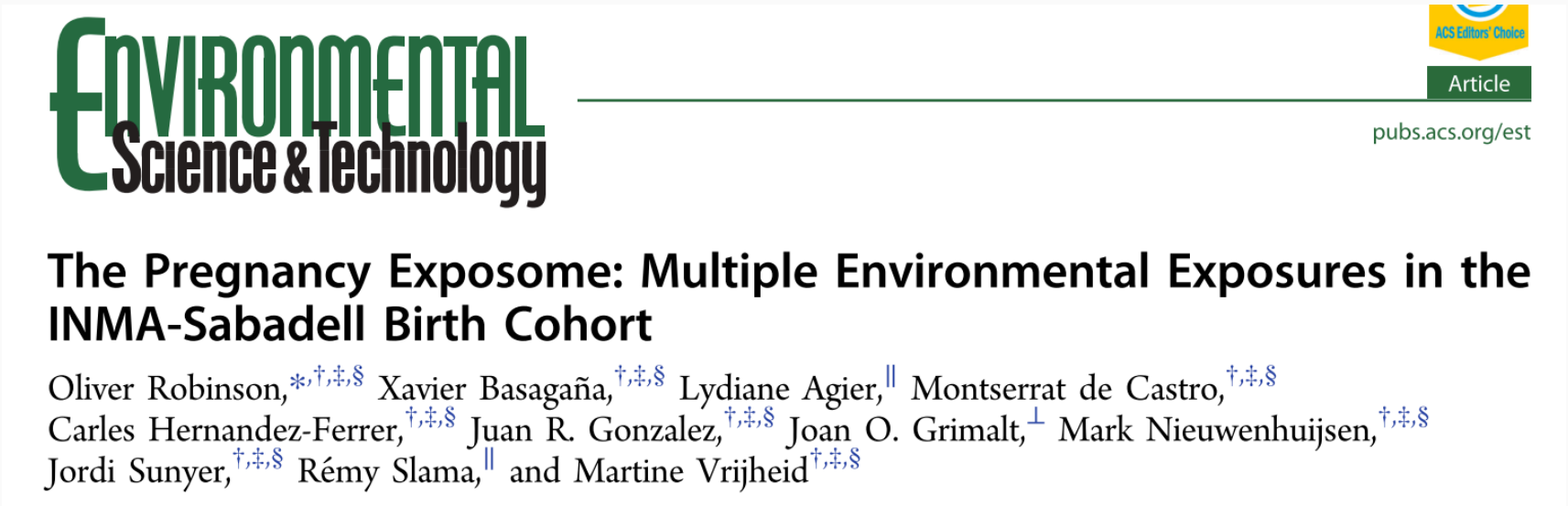
Molecular epidemiology:

- omics technologies to study internal components of exposure, identify early responses to exposure and produce exposure profiles;
- part of a wider trend towards the 'molecularisation' of medicine (Boniolo and Nathan, 2017);
- considered "frontier research", highly multidisciplinary and innovative (Illari and Russo, 2016)

Molecular Epidemiology in Practice: Exposome Research

- For example, exposome research:
  - global approach to exposure, distinguishing between internal and external components (the 'exposome');
  - search for biomarkers, i.e. elements of the environment or the organism that can be measured and in turn used to trace exposure;
  - Meet-In-The-Middle approach (MITM): when disease and external components of exposure are associated, their relationship is studied by searching for intermediate biomarkers of internal components of exposure, lying *in the middle* of the relation.
- Recent projects: EnviroGenomarkers (2009-2013), EXPOsOMICS (2012-2017), Lifepath (2015-2019), all funded by the European Union.

Data in Molecular Epidemiology



Environmental Science & Technology

ACS Editors' Choice

Article

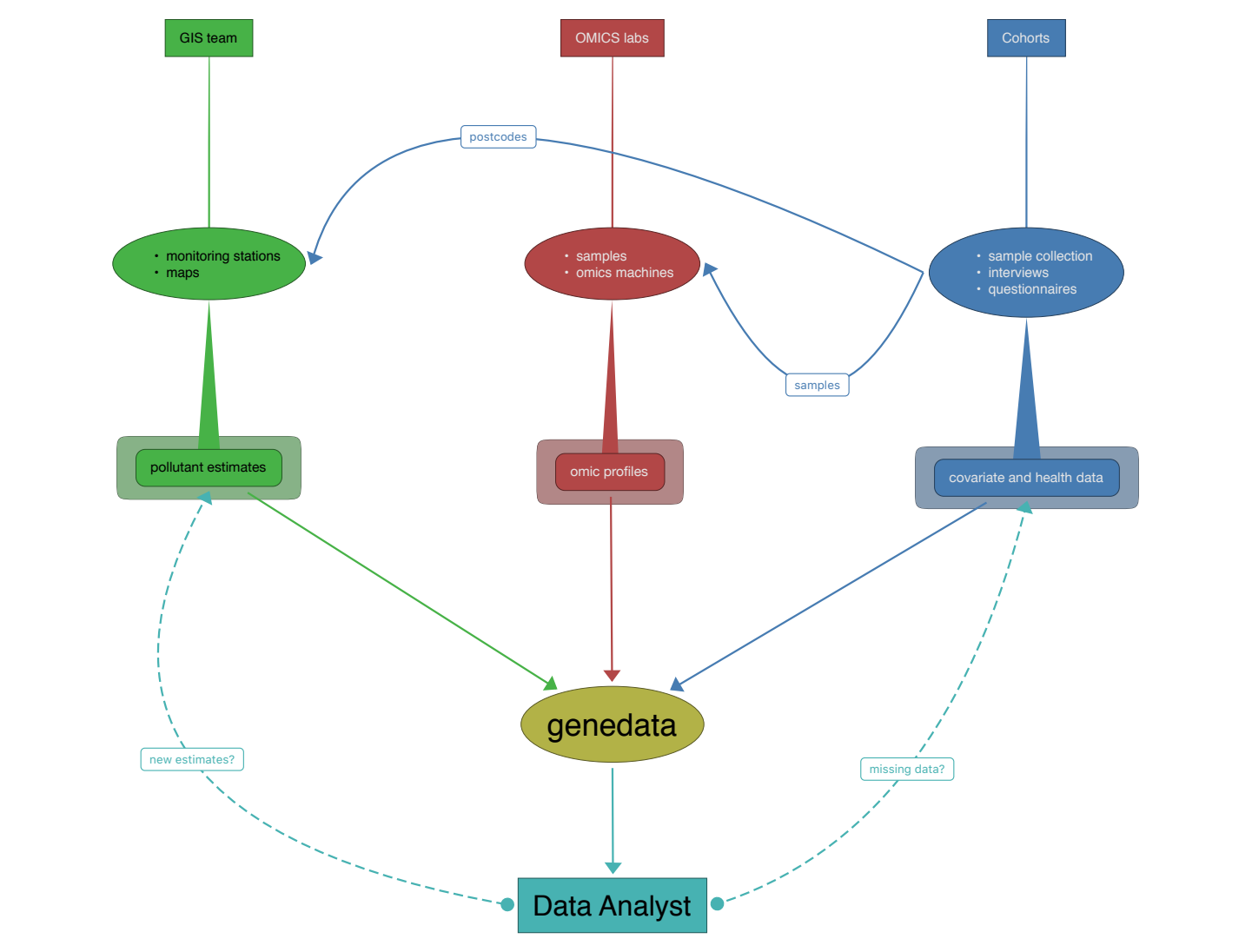
pubs.acs.org/est

The Pregnancy Exposome: Multiple Environmental Exposures in the INMA-Sabadell Birth Cohort

Oliver Robinson,[*,†,‡,§] Xavier Basagaña,[†,‡,§] Lydiane Agier,[∥] Montserrat de Castro,[†,‡,§] Carles Hernandez-Ferrer,[†,‡,§] Juan R. Gonzalez,[†,‡,§] Joan O. Grimalt,[⊥] Mark Nieuwenhuijsen,[†,‡,§] Jordi Sunyer,[†,‡,§] Rémy Slama,[∥] and Martine Vrijheid[†,‡,§]

- exposome during pregnancy;
- INMA (INfancia y Medio Ambiente) birth cohort, based in Spain.

Data in Molecular Epidemiology



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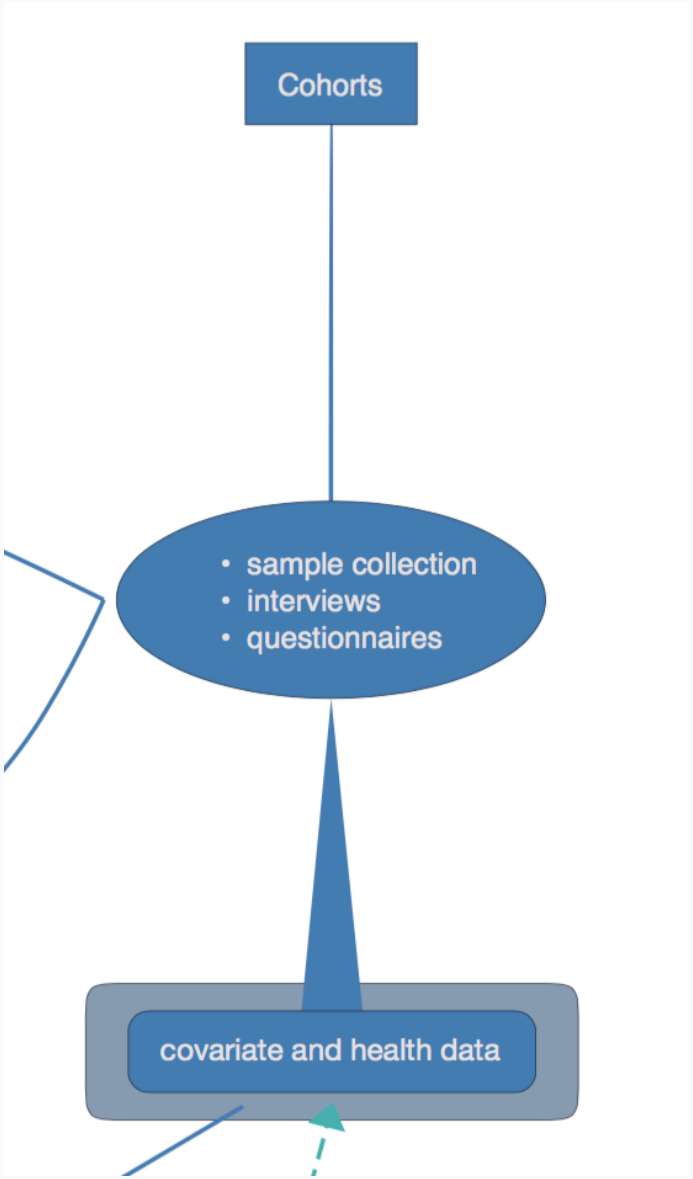

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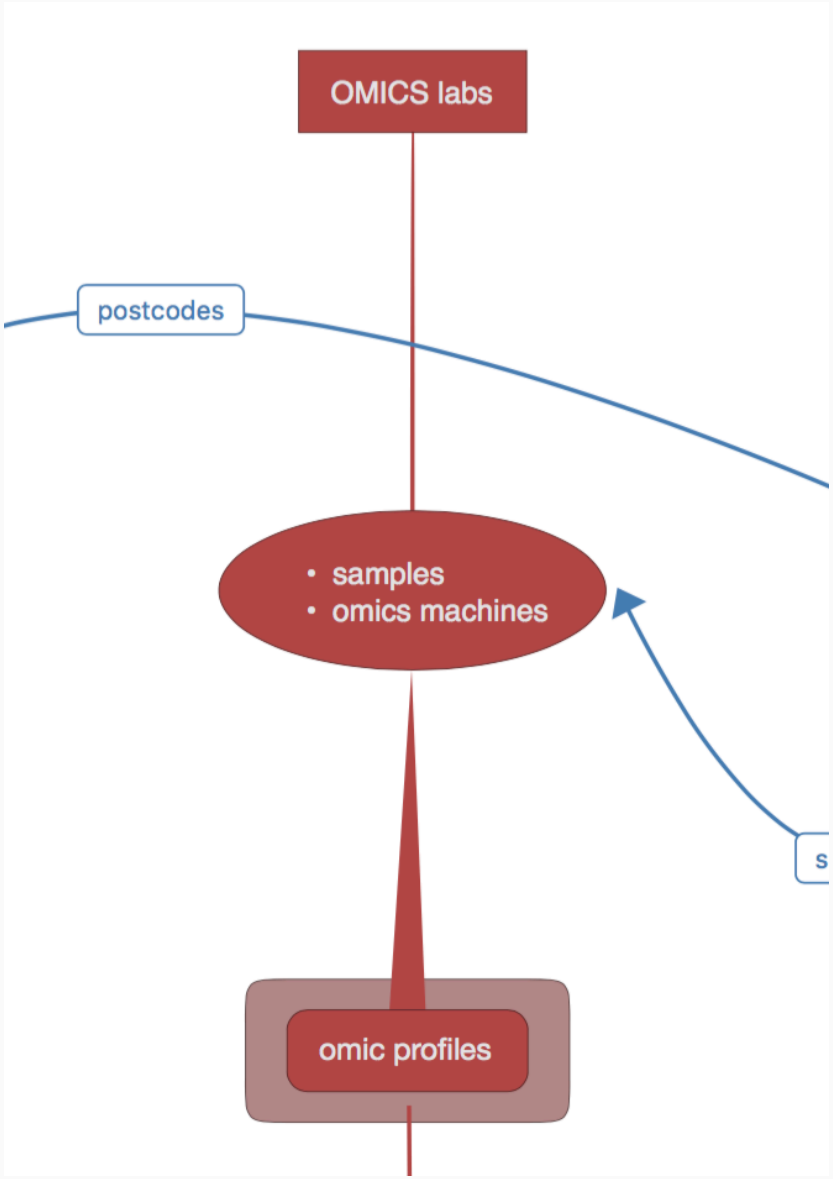

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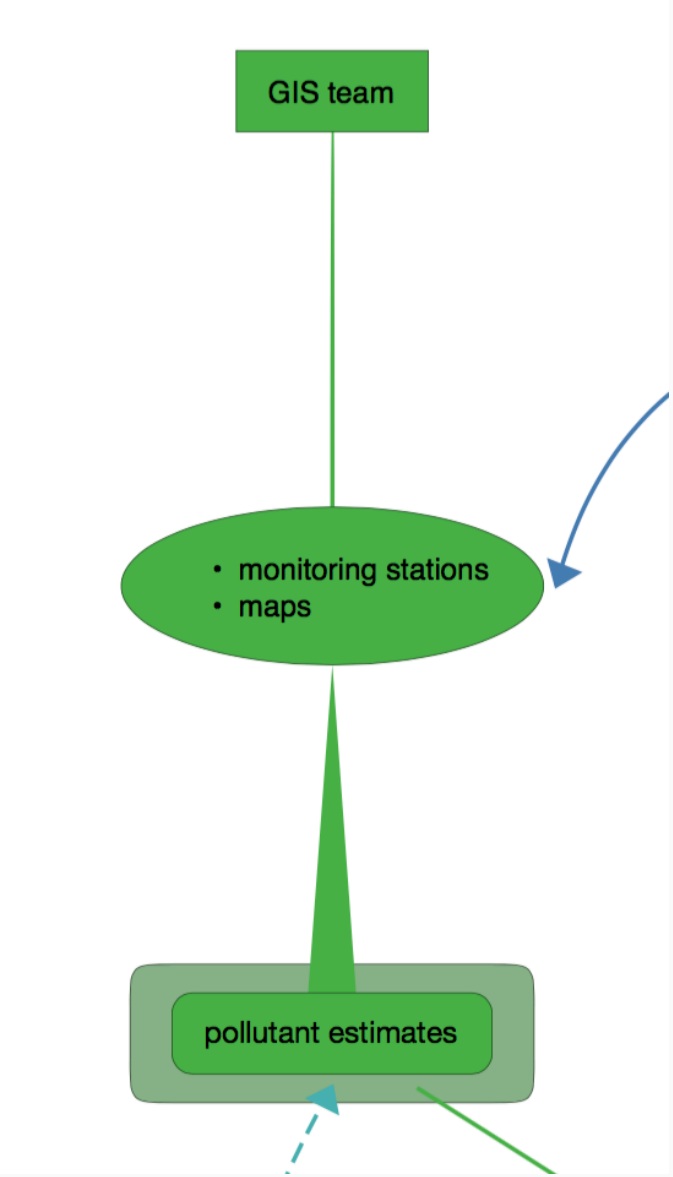

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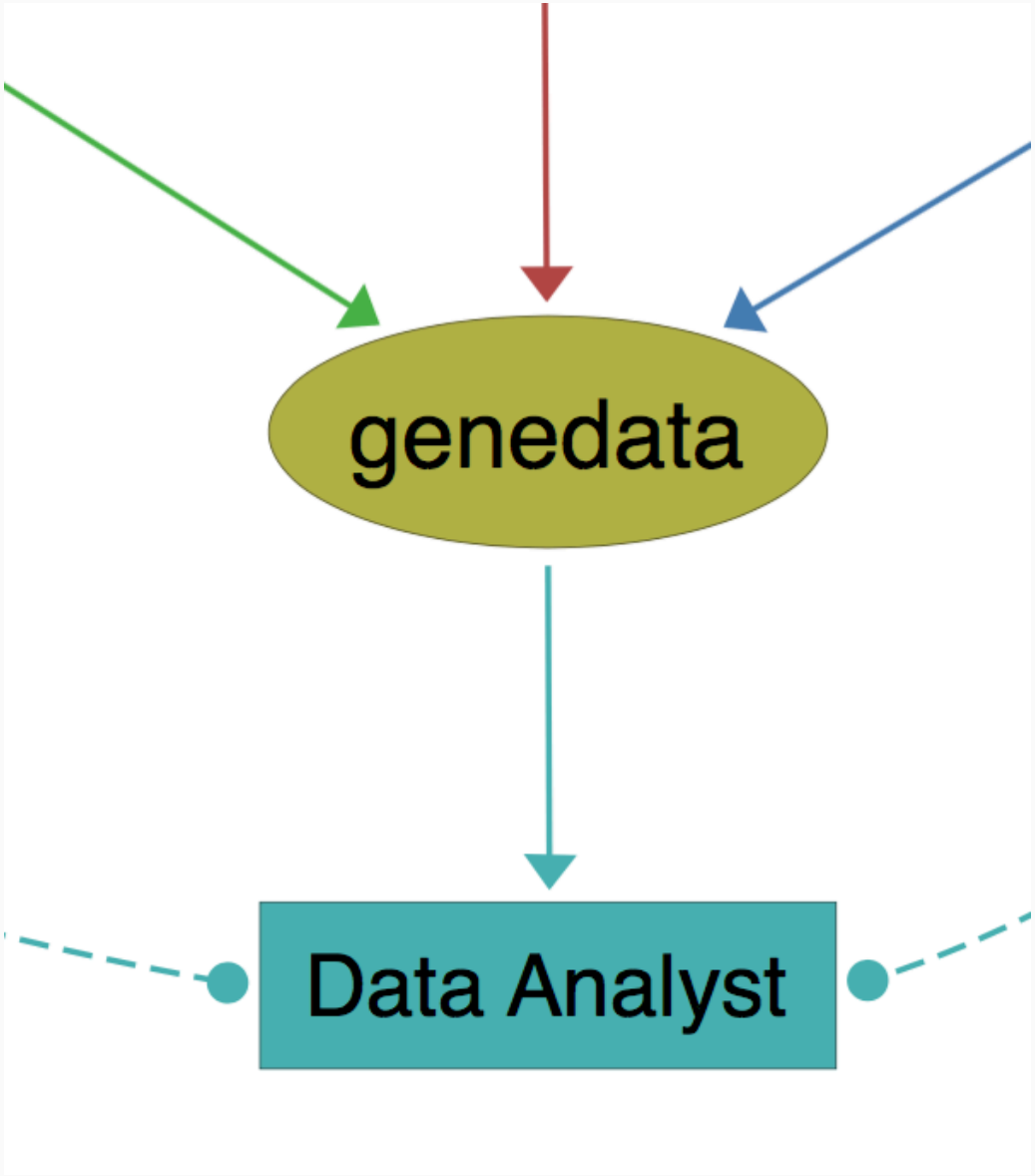


Molecular Epidemiology as a Data-Intensive Science Example

Molecular epidemiology as an example of data-intensive science according a broad definition of big data (Kitchin, 2014).

Researchers certainly benefit from the volume, velocity and variety of their datasets (both health and sociodemographic data).

The high level of resolution made possible by omics technologies allow epidemiologists study exposure at both external and internal levels.

The possibility of conjoining different types of datasets is another key feature.

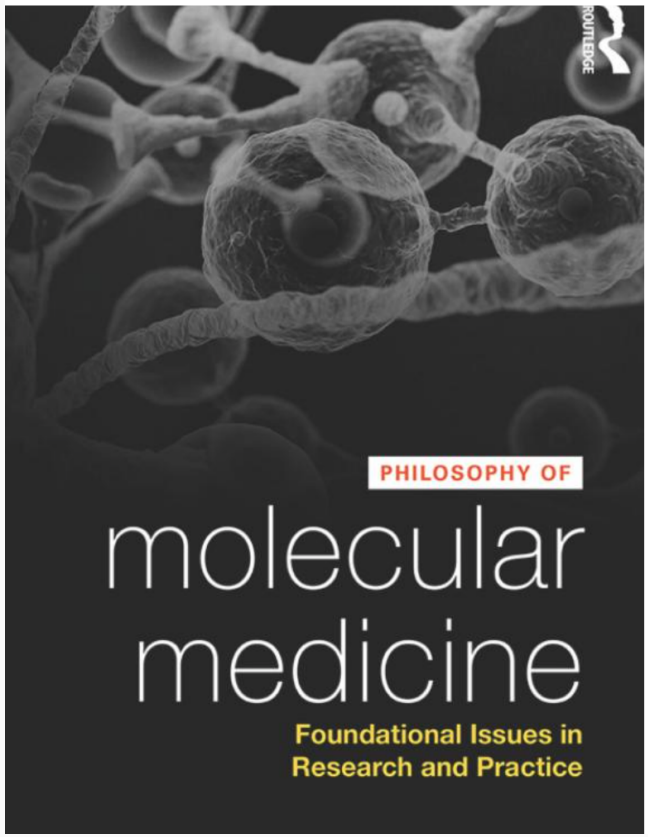
2. Epistemological Aspects of Molecular Epidemiology

Philosophical Interest in the Discipline

Topoi (2016) 35:175–190
DOI 10.1007/s11245-013-9228-1

Information Channels and Biomarkers of Disease

Phyllis Illari · Federica Russo



12 Opportunities and Challenges of Molecular Epidemiology

Federica Russo and Paolo Vineis

Vineis *et al. Emerg Themes Epidemiol (2017) 14:7*
DOI 10.1186/s12982-017-0061-7

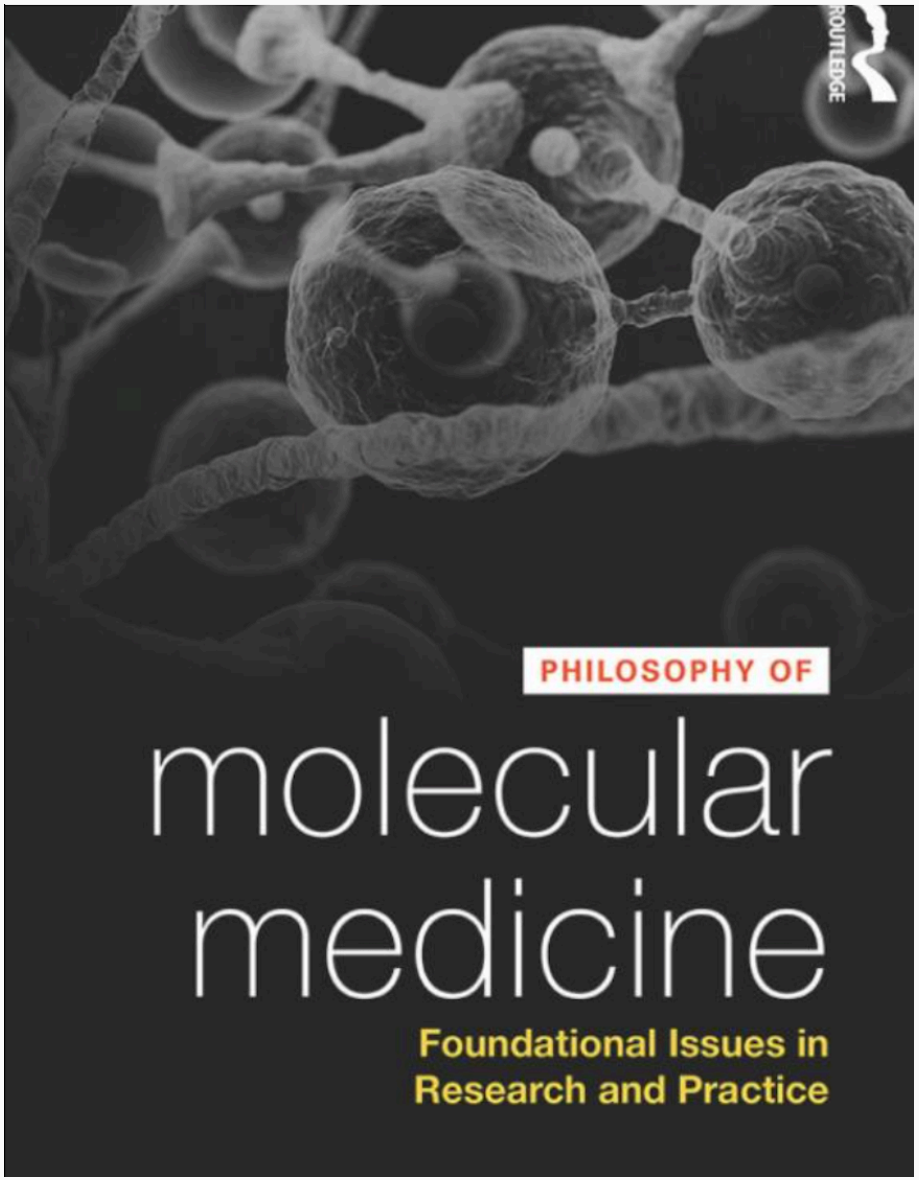
Emerging Themes in Epidemiology

COMMENTARY Open Access

Causality in cancer research: a journey through models in molecular epidemiology and their philosophical interpretation

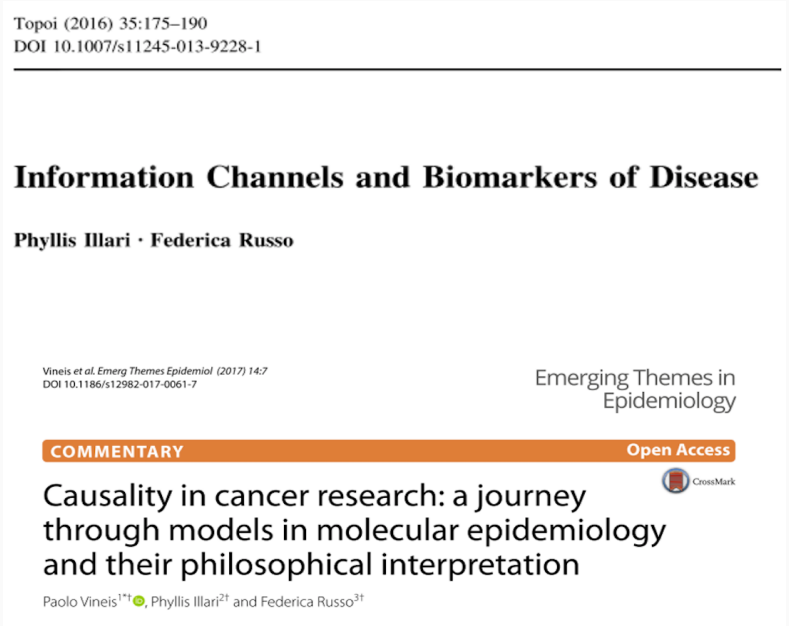
Paolo Vineis[1*†], Phyllis Illari[2†] and Federica Russo[3†]

Context: Molecularisation of the Health Sciences



- use of omics technologies in various disciplines in the health sciences;
- changing notion of disease;
- micro-macro relations.

Philosophy of Causality



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Paolo Vineis[1*†], Phyllis Illari[2†] and Federica Russo[3†]

- new causal production view;
- idea of causal linking;
- information transmission account of causal production.

Epistemological Aspects

12 Opportunities and Challenges of Molecular Epidemiology

Federica Russo and Paolo Vineis

- changes in the scale of measurement;
- changes in what can be traced and measured;
- changes in the kinds of evidence that can be produced.

3. Causal Inference in Molecular Epidemiology

Towards a New Kind of Causal Inference?

"By changing the scale of measurement, molecular epidemiology improves on traditional epidemiology also in another important respect: it goes beyond associations and is in principle able to shed light on the *mechanisms* of disease causation, rather than just hypothesize them, because it can make appropriate tests"

— Russo and Vineis (2017)

Russo and Vineis' View

Russo and Vineis' argument: the availability of omics technologies makes it possible to study disease at the molecular level, allowing epidemiologists to produce mechanistic evidence, on the basis of which they make causal claims.

- Molecular epidemiologists produce both difference-making (associations between external biomarkers of exposure and internal biomarkers of disease) and mechanistic evidence (intermediate biomarkers of early responses to external exposure).
- Novelty for epidemiology, which has traditionally focused on evidence of correlations and associations in order to make causal claims, rather than evidence of mechanisms.
- Example of Russo and Williamson's thesis (RTW): both evidence of underlying mechanisms and evidence of causes making a difference to effects are provided.

My Take on This

My take, in three points:

1. causal inference in molecular epidemiology does not give a special role to mechanistic evidence;
2. causal inference in molecular epidemiology is not as novel as suggested;
3. the RTW holds, but at a higher level than epidemiology and has to be seen from a multidisciplinary perspective on the health sciences;

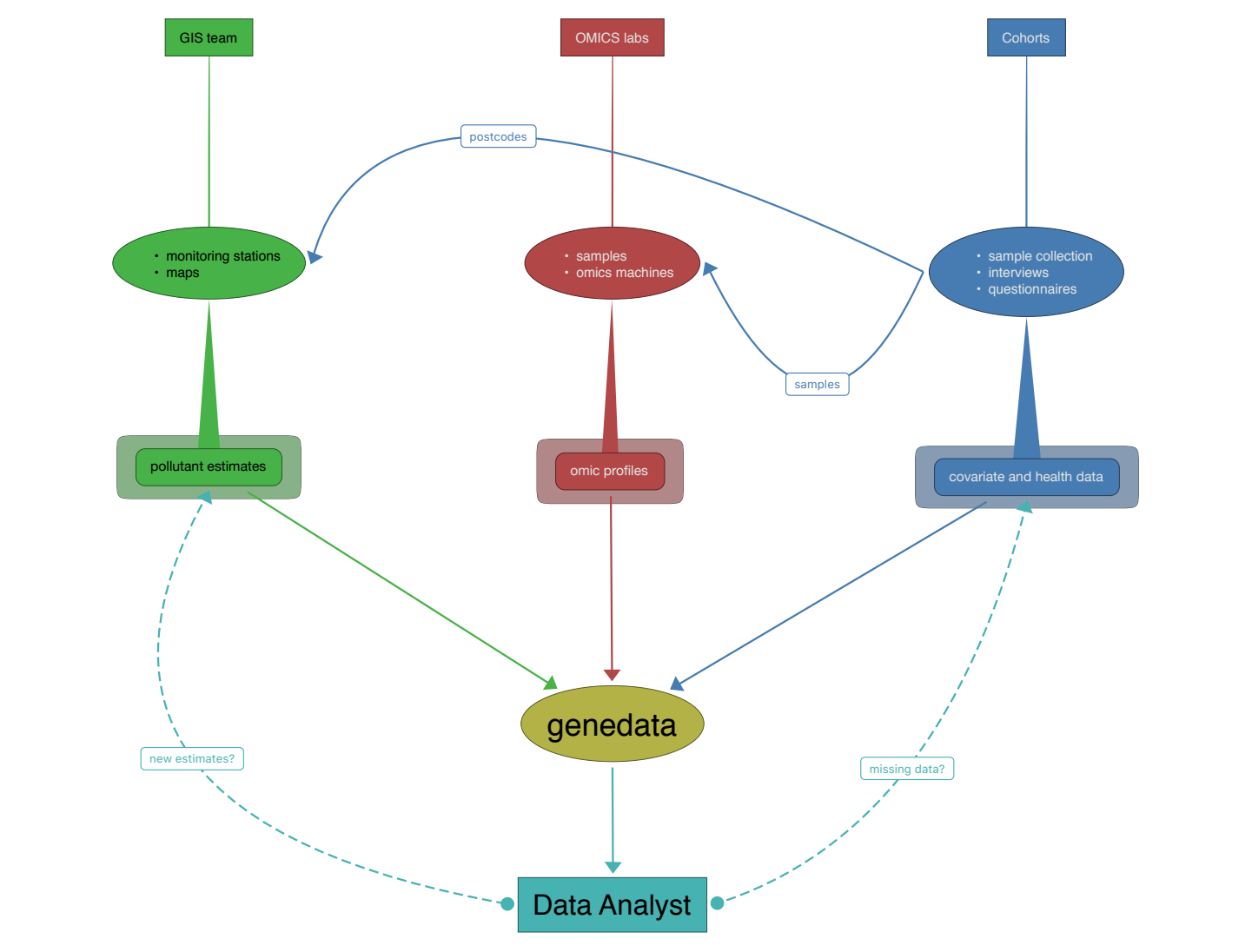
1. Which Kind of Evidence is Produced in Molecular Epidemiology?

I am not sure that the kind of evidence produced by molecular epidemiologists is mechanistic.

Russo and Vineis (2017) seem to suggest that what is able to "shed light on the *mechanisms* of disease causation" is the work on intermediate biomarkers.

However, digging into the work done with these biomarkers, it's not clear to me how this is mechanistic evidence.

1. Which Kind of Evidence is Produced in Molecular Epidemiology?



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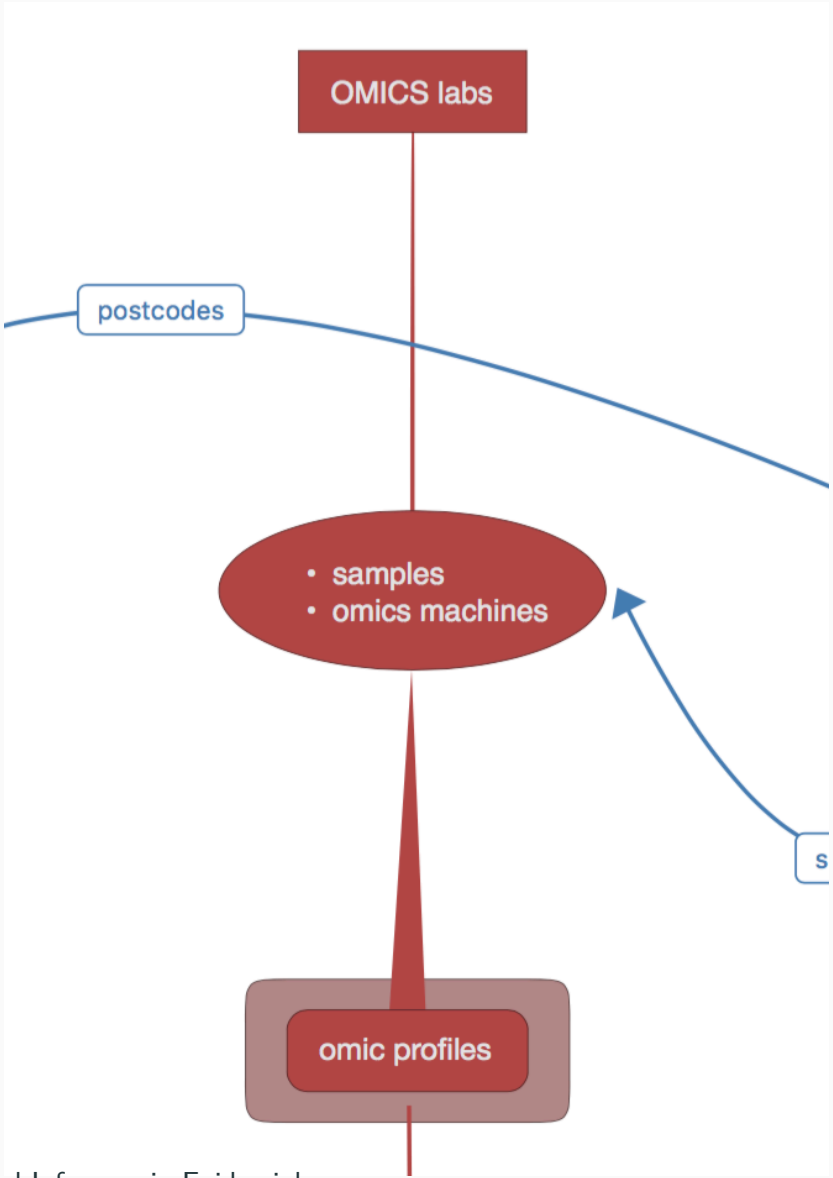

1. Which Kind of Evidence is Produced in Molecular Epidemiology?

So, what are these exposure profiles/levels?

Exposure
Perfluorohexane sulfonic acid
Perfluorooctanoic acid
Perfluorooctane sulfonic acid
Perfluorononanoic acid
Dichlorodiphenyldichloroethylene
Hexachlorobenzene
β-hexachlorocyclohexane
Polychlorinated biphenyl - 153
Polychlorinated biphenyl - 180
Polychlorinated biphenyl - 138
Polybrominated diphenyl ether -47
Polybrominated diphenyl ether -100
Polybrominated diphenyl ether -99
Polybrominated diphenyl ether -85
Polybrominated diphenyl ether -154
Polybrominated diphenyl ether -153
Polybrominated diphenyl ether -183
Polybrominated diphenyl ether -209

Mercury
Cobalt
Nickel
Asenic
Copper
Zinc
Selenium
Molybdenum
Cadmium
Antimony
Cesium
Thallium
Lead
Mono-(2-ethylhexyl) phthalate

1. Which Kind of Evidence is Produced in Molecular Epidemiology?

Exposure profiles essentially track the presence of pollutants at the molecular level.

These biomarkers are tracking the presence/absence of pollutants and thus the levels and difference that pollutants bring about.

Intermediate biomarkers, through exposure profiles, are not tracking mechanisms.

Epidemiologists in the project don't speak of mechanisms, nor mechanistic evidence.

1. The Role of Mechanistic Evidence in Molecular Epidemiology

Does this mean that mechanistic evidence plays no role in molecular epidemiology?

Quite the opposite:

- information about known disease mechanisms used when designing studies;
- known mechanisms used as proxies to measure the cumulative effect of exposure;
- mechanistic evidence used to assess results obtained from data analysis.

However, evidence of mechanisms does not seem to play a special nor new role in molecular epidemiology, as compared to more traditional epidemiology.

2. The Novelty of Causal Inference in Molecular Epidemiology

Novel aspects of casual inference in molecular epidemiology: scale of measurements, new sources of data, advancement on the statistical side.

Some novelties related to the kinds of evidence used for causal inference, but no major nor new role played by mechanistic evidence.

Approaches like the MITM are innovative – I just wouldn't say as innovative as Russo and Vineis argue, or at least not in their sense.

3. The RTW and Molecular Epidemiology

Does this undermine Russo and Vineis' application of the RWT to molecular epidemiology?

See also Broadbent on RWT: "this claim may be theoretically interesting, but it adds little from a practical perspective" (Broadbent, 2013, p. 68).

I don't agree with Broadbent and I think that the RWT holds, but there are a few elements to consider, which suggest an important feature of the RTW.

The RWT should be considered as a claim about the health sciences collectively considered and not necessarily about single disciplines, like epidemiology.

3. The RTW and Molecular Epidemiology

Mechanistic evidence is indeed required to make causal claims in the health sciences, but this is often provided by other disciplines than molecular epidemiology:

- epidemiologists use mechanistic evidence to inform their research on disease causation;
- since they're mostly using difference-making evidence, they're very cautious about making causal claims (see also Broadbent on causal interpretation);
- their results provide directions for further research and prioritise some hypotheses, which will be further explored by looking for mechanistic evidence through for instance animal experiments, lab work, etc.
- mechanistic evidence provided by other disciplines is considered the ultimate way of looking at causality by epidemiologists themselves.

3. The RTW and Molecular Epidemiology

Thus, we shouldn't necessarily think of causal inference as a monolithic endeavour in the health sciences, but rather as a multidisciplinary one.

The RWT rightly frames this endeavour in terms of different kinds of evidence: these kinds of evidence may be provided by different disciplines.

Conclusions

The Take-Home Message

In this talk, I have:

- focused on advances in medicine, by looking at molecular epidemiology and exposome research;
- argued against new causal inference approaches as novelties in the field;
- argued in favour of seeing causal inference as a multidisciplinary endeavour in the life sciences.

Take-home message:

> epidemiology provides one of the necessary pieces to solve the puzzle of disease causation: for the puzzle to be solved, different kinds of evidence have to be provided by different disciplines.

Thanks for the attention!