Hypotheses vs. Evidence

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Scientific knowledge is in perpetual evolution; it finds itself changed from one day to the next.

(Jean Piaget)

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The good news:

➢ Despite being a rare disease, awareness is growing globally.

➢ Awareness for:

      ➢ Symptoms

      ➢ Diagnosis

      ➢ Treatment

➢ Resulting in more cases reported but with excellent prognosis and low mortality

➢ Early diagnosis results in simple and effective treatment in most of the cases.
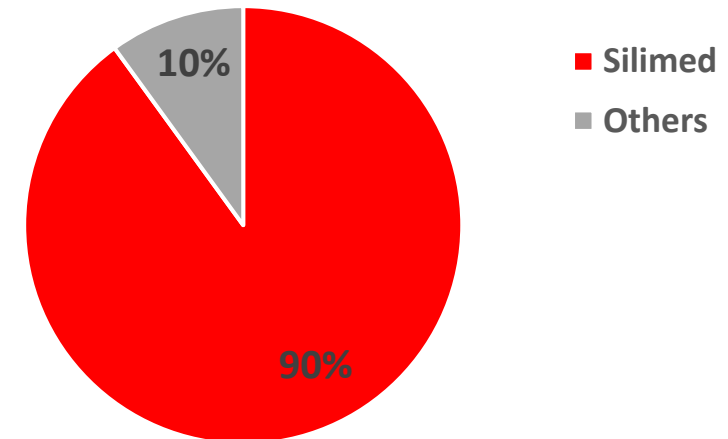
The good news:

➤ Based on the data available today and when implant surface is known-

    ➤ Among textured silicone implants, Allergan implants account for 80.7%-90.9% of cases. (FDA)

    ➤ Among Polyurethane covered implants, Silimed implants in Australia account for ~90% of cases (Loch-Wilkinson, 2019)

% of BIA-ALCL cases in textured implants

~15%

~85%

■ Allergan
■ Others

FDA
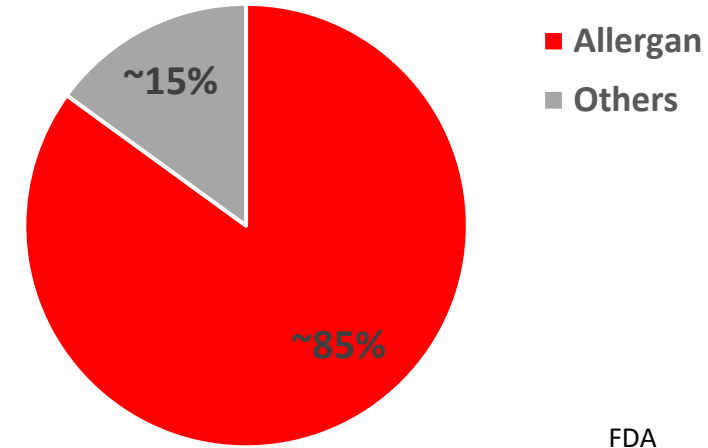
% of BIA-ALCL cases in polyurethane covered implants

10%

90%

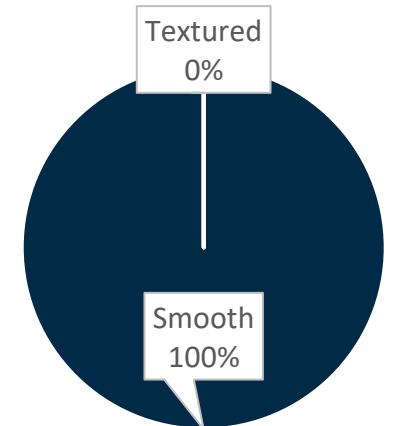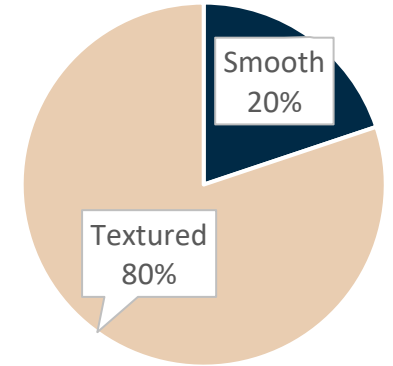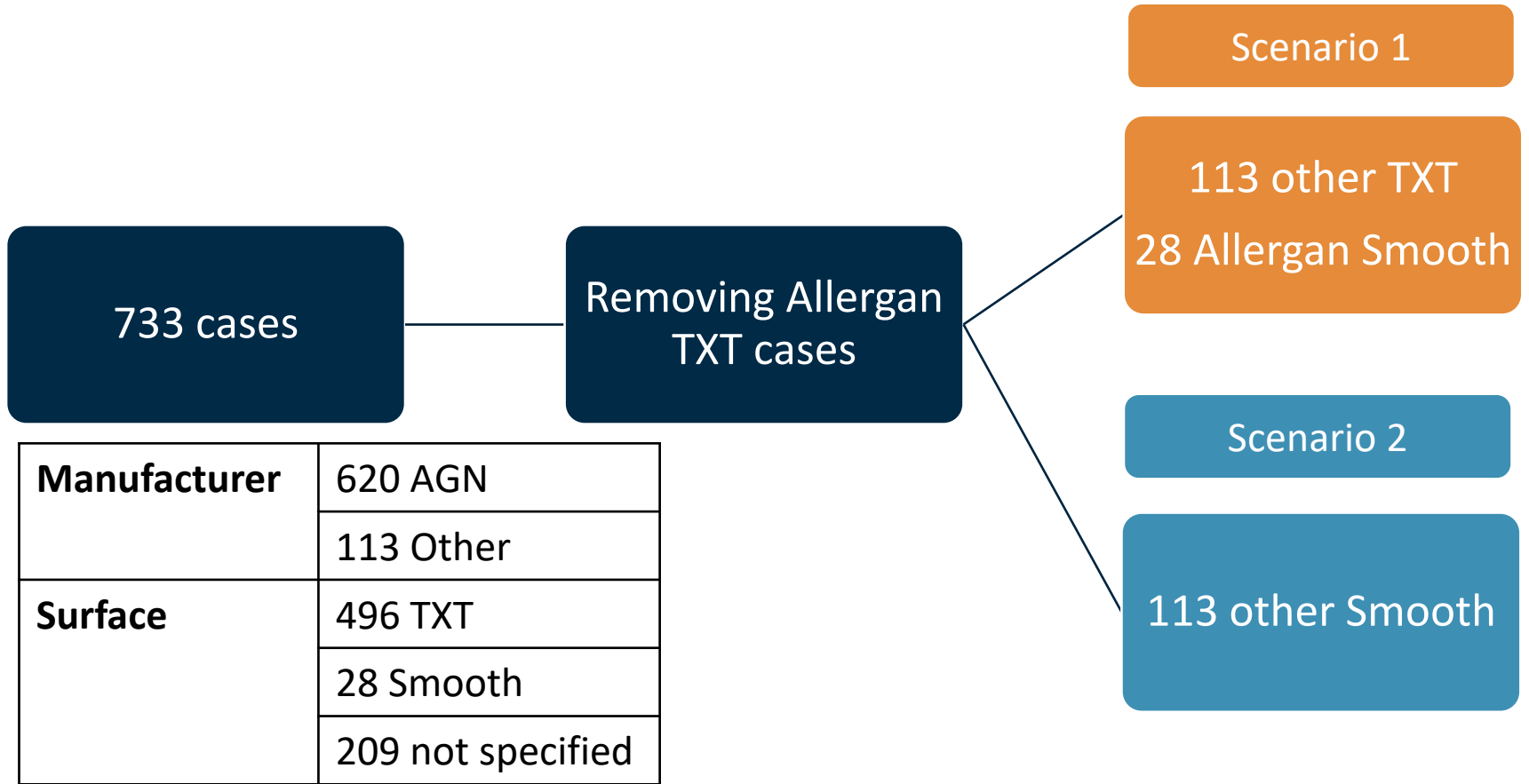■ Silimed
■ Others

Loch-Wilkinson, 2019

Why is this good news?

➤ These two specific implant types have been removed from the world market and are not being implanted any more*.

➤ The many benefits of non-smooth implants can be realized when indicated, while lowering the risk of BIA-ALCL significantly.

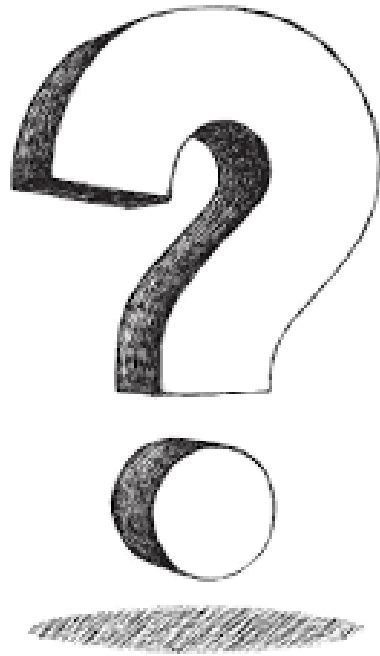* Silimed polyurethane implants are still in use in parts of South America

Now, lets look again at the 2020 FDA data (without Allergan Textured)

733 cases

Removing Allergan TXT cases

Manufacturer	620 AGN
	113 Other
Surface	496 TXT
	28 Smooth
	209 not specified

Scenario 1

113 other TXT
28 Allergan Smooth

Smooth 20%

Textured 80%

Scenario 2

113 other Smooth

Textured 0%

Smooth 100%

Two extreme scenarios of surface distribution:
Smooth represent between 20%-100% of non-Allergan-Textured cases

The bad news

There is much we (still) don't know….

Some open questions

*bubble size does not represent importance

Leading hypotheses

- Shell Shedding Particles
- Leachables
- Friction
- Genetic Predisposition
- Bacterial contamination
- Other...
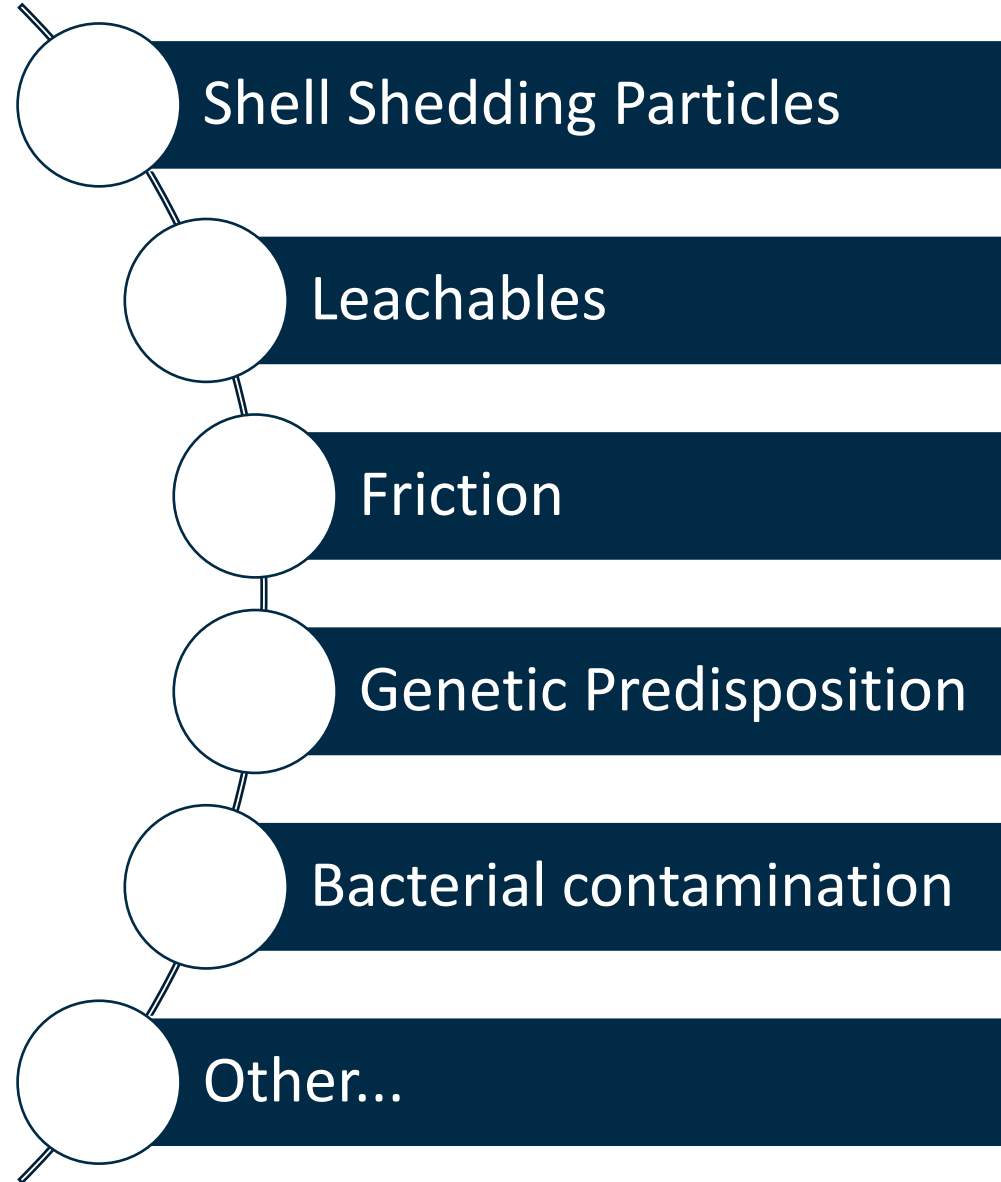
+ Time

No proven mechanism

Why is there so much confusion?

Relevant

- Emerging disease
- Science is an evolutionary process
- Incidence is very low
- Multifactorial
- Data collection is not standardized
- Geographical variation

Political

- Limited access to raw data
- Irrelevant agendas
- Pressure to come up with simple answers
- Vested interests
- Public Scrutiny
- Preconceived stereotypes about patients

Some thoughts about surface characterization

What is surface characterization?

A method to create standardized descriptive measures of relevant surface properties.

Specific properties are chosen based on the goal of the characterization.

Typically focuses on one or more of these property families:

➢ Morphology

➢ Chemistry

➢ Mechanical

➢ Optical

➢ Thermo-dynamic

> "Few techniques actually are able to provide surface data of direct relevance to the biological implant environment"
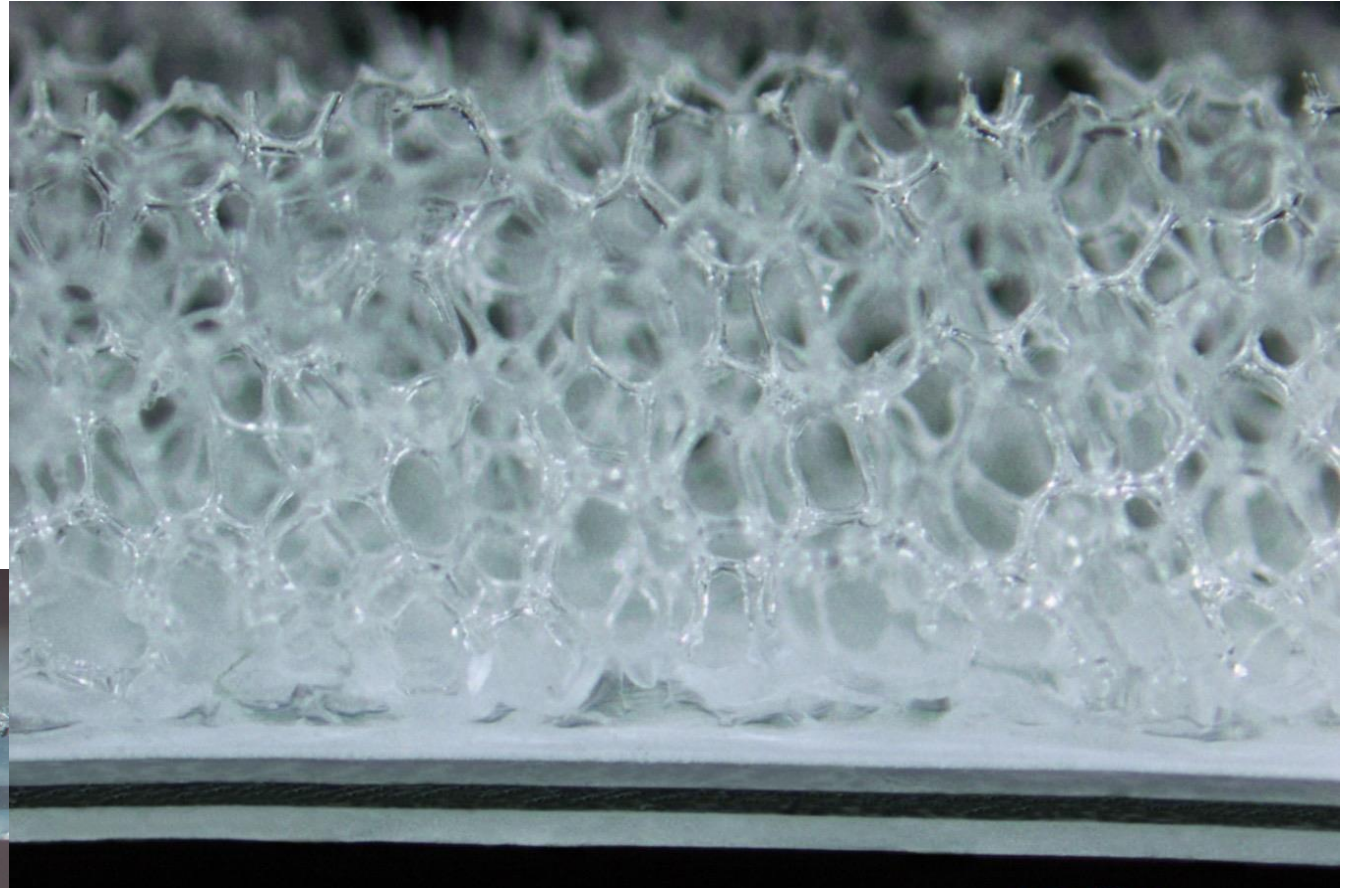> (Grainger et al, in Ducheyne, P.(2015).
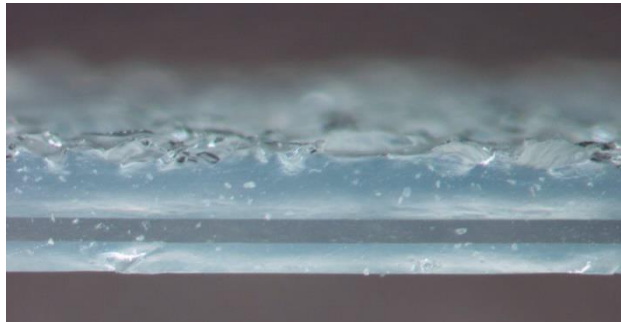> *Comprehensive biomaterials* (Vol. 1). Elsevier).

Analytical measurement tools are chosen based on the property and desired resolution.

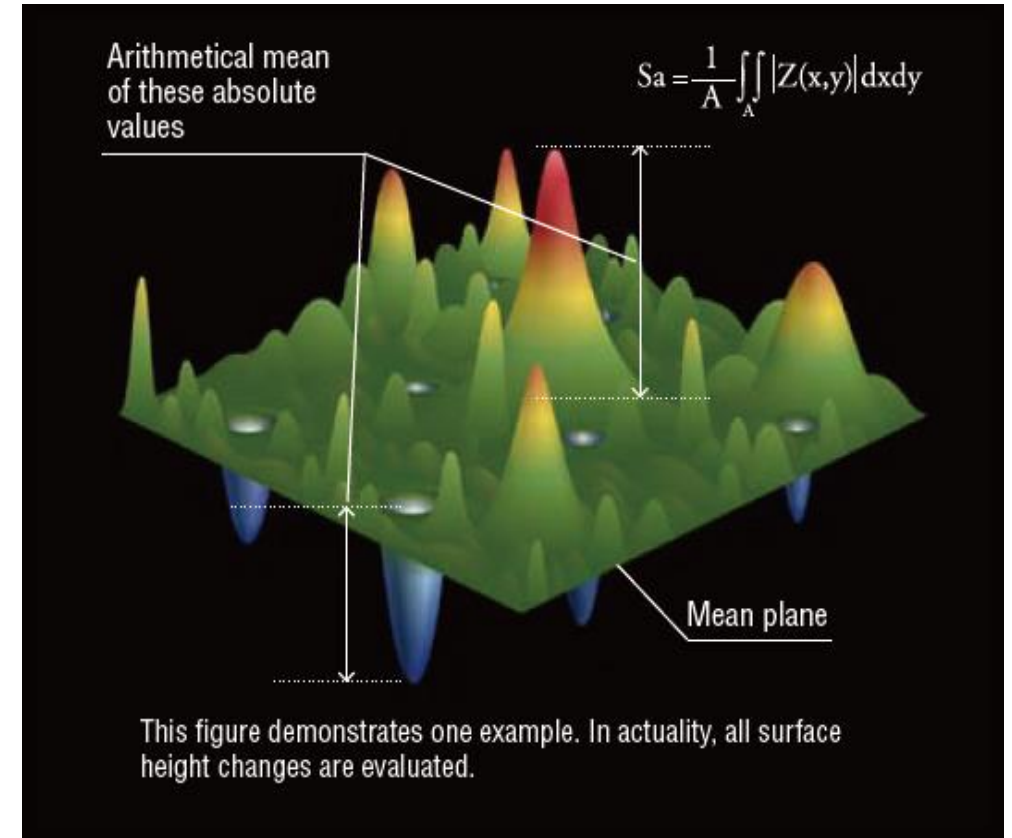# Comparing Apples to Oranges:

3D PU Topology

2D Silicone Texture

Main Morphologic Features of 2D Surfaces (Smooth or Textured Silicone Implants)

Parameter	Description
Arithmetic mean height	absolute value- the difference in height of each point compared to the arithmetical mean of the surface
Root mean square height	equivalent to the standard deviation of heights
Skewness	degree of bias of the roughness shape (asperity)
Kurtosis	measure of the sharpness of the roughness profile
Texture direction	represents the lay of the surface texture
Density of peaks	number of peaks per unit area

Arithmetical mean of these absolute values

$$Sa = \frac{1}{A} \iint_A |Z(x,y)| \, dxdy$$

Mean plane

This figure demonstrates one example. In actuality, all surface height changes are evaluated.

https://www.keyence.com/ss/products/microscope/roughness/surface/parameters.jsp

Main Morphologic Features of 3D Porous Scaffolds (PU-Covered Implants)

Parameter	Description
Porosity	Porosity = pore volume/specimen volume × 100%
Interconnectivity	Interconnectivity = interconnected pores volume/total porosity volume
Pore size	Mean pore diameter
Anisotropy	Nonhomogeneity in the alignment of scaffold struts
Cross-section area	Measure of the area in a section of the scaffold
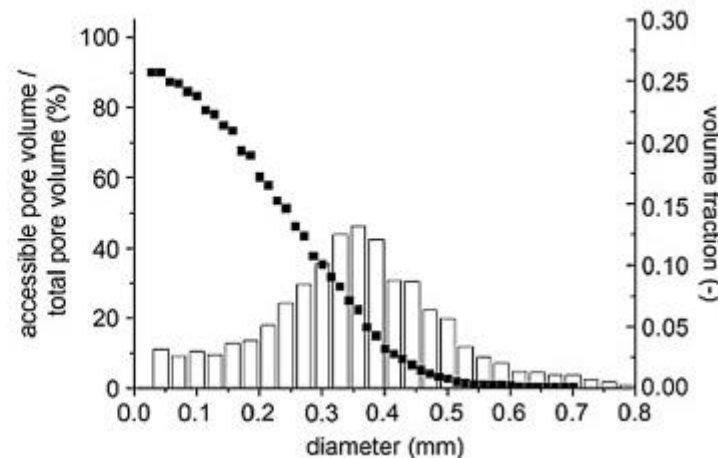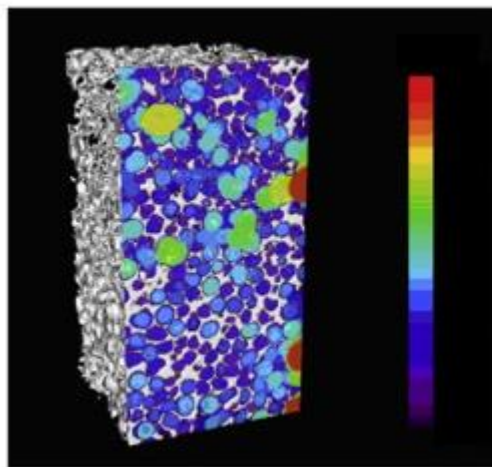
Bertoldi et al- J Appl Biomater Biomech 2011; Vol. 9 no. 3, 165-175

Dietmar W. et al (2014), in Tissue Engineering (2nd Edition) Chapter 10 - Scaffold Design and Fabrication, P 311-346,

X140
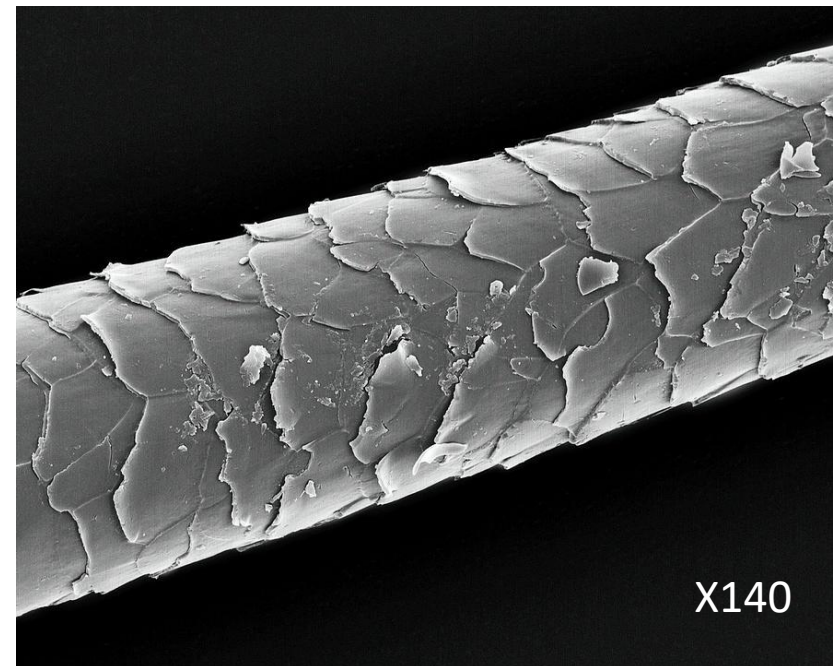
Human Hair With Damaged Cuticle is a photograph by Dennis Kunkel Microscopy/science Photo Library which was uploaded on September 25th, 2018.

Some thoughts about causality and risk factors

In statistics, the phrase "**correlation does not imply causation**" refers to the inability to legitimately deduce a cause-and-effect relationship between two variables solely on the basis of an observed association or **correlation** between them

 Aldrich, John (1995). *"Correlations Genuine and Spurious in Pearson and Yule"*. *Statistical Science*. **10** (4): 364-376.

tylervigen.com

New Cases/Year

18.1M
Cancer

Carcinoma

Other Cancers

1M
Lymphoma

Hodgkin

700k
Non-Hodgkin

Other

10.2k
ALCL

159
BIA-ALCL
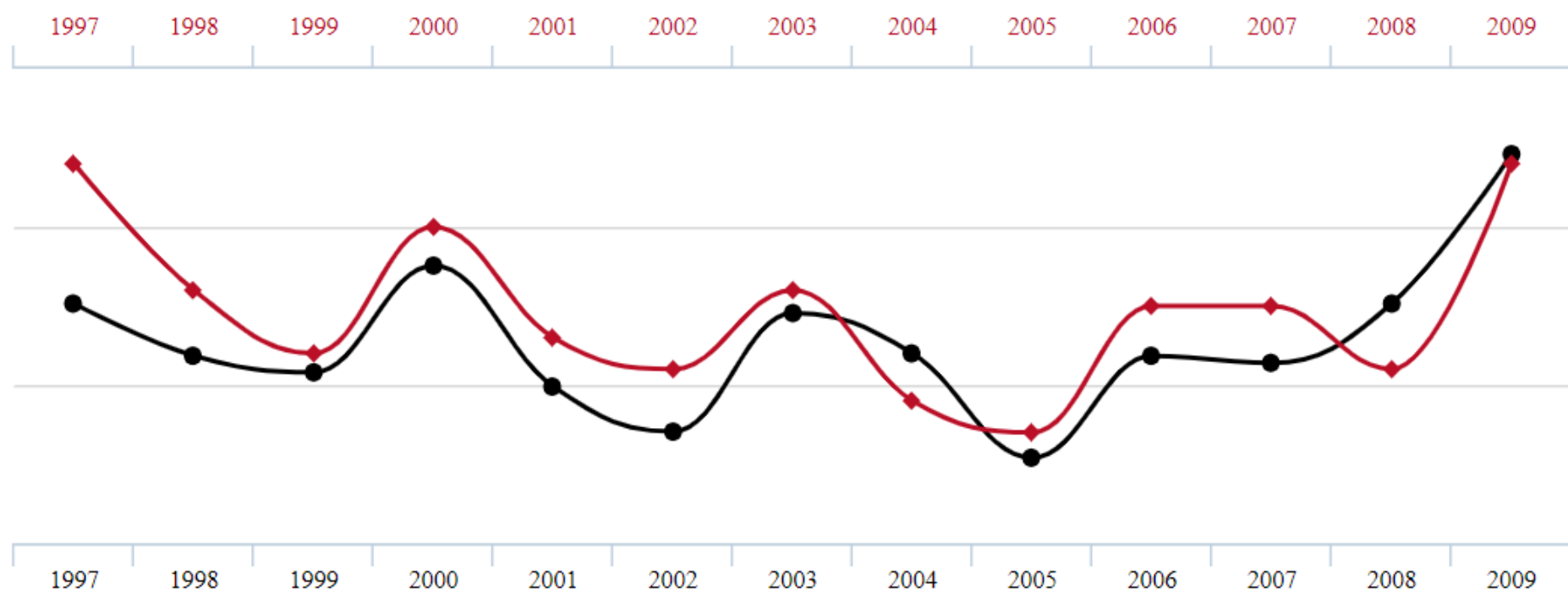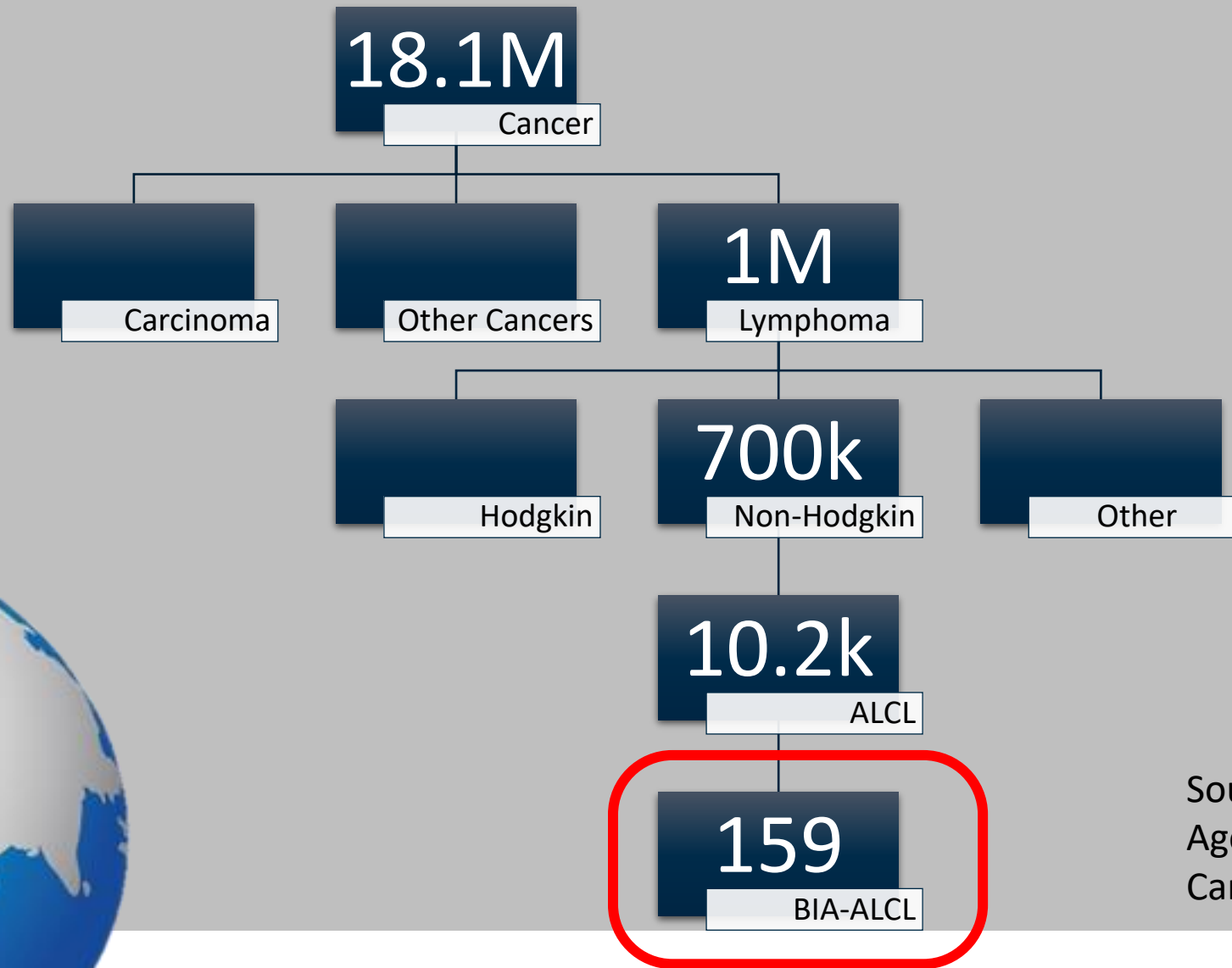
Source: WHO: International Agency for research on Cancer, accessed: 10/2019

Some Known Risk Factors for NHL

Infections

Some viruses or bacteria increase the risk of developing NHL

Weakened Immune System

e.g. HIV or use of immunosuppressants

Autoimmune disease

Not known if disease or treatment
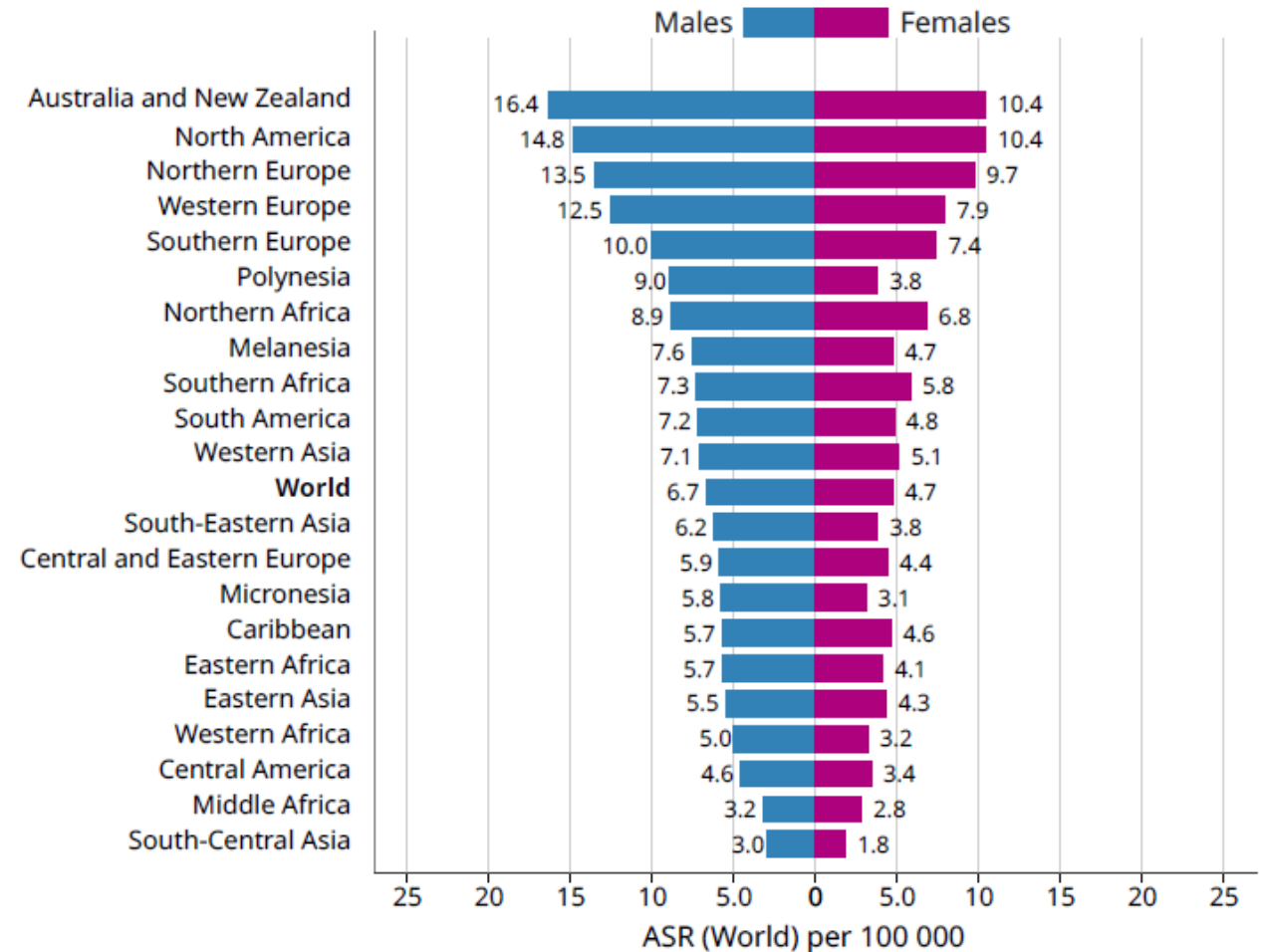
Previous cancer

Possibly the disease or treatment (chemotherapy, radiotherapy)

Having a close relative with NHL

3% vs. 2% lifetime risk

Age standardized (World) incidence rates, non-hodgkin lymphoma, by sex

Region	Males	Females
Australia and New Zealand	16.4	10.4
North America	14.8	10.4
Northern Europe	13.5	9.7
Western Europe	12.5	7.9
Southern Europe	10.0	7.4
Polynesia	9.0	3.8
Northern Africa	8.9	6.8
Melanesia	7.6	4.7
Southern Africa	7.3	5.8
South America	7.2	4.8
Western Asia	7.1	5.1
World	6.7	4.7
South-Eastern Asia	6.2	3.8
Central and Eastern Europe	5.9	4.4
Micronesia	5.8	3.1
Caribbean	5.7	4.6
Eastern Africa	5.7	4.1
Eastern Asia	5.5	4.3
Western Africa	5.0	3.2
Central America	4.6	3.4
Middle Africa	3.2	2.8
South-Central Asia	3.0	1.8

ASR (World) per 100 000

Some thoughts about next steps

"No raw data, no science"

Tsuyoshi Miyakawa

Next steps

- Already removed strongest association known. Follow up to verify.

- Collect Exhaustive epidemiological information:

  Improve Retrospective Data:

  - Thorough investigation on all reported cases to date (case by case).

  Collect Data Prospectively:

  - Globally Networked Local Registries

  - Systematic collection and analysis of tissues and implants of BIA-ALCL patients

- Make raw data freely available to scientific community

Learn from others, e.g.- EBMT

Continue the efforts to increase awareness:
- Patients
- Surgeons
- Health care providers

Thank you!

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