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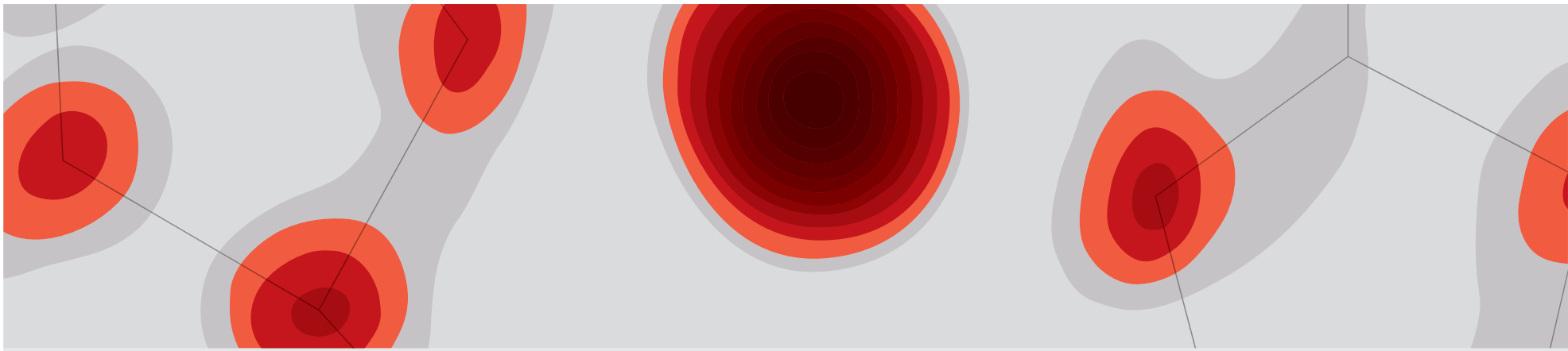

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- Cell Death & Disease
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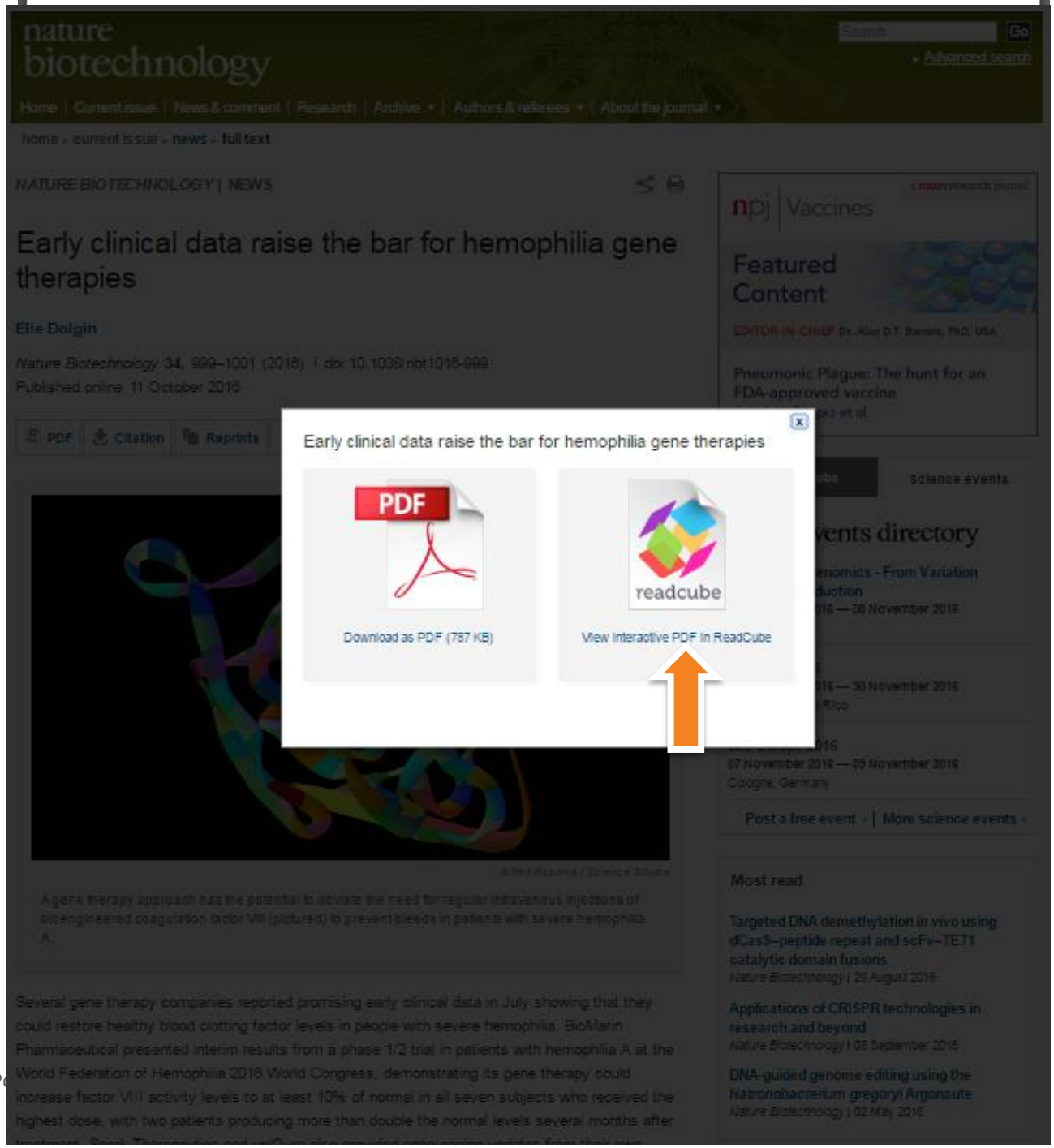
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Early clinical data raise the bar for hemophilia gene therapies
Elie Dolgin
Nature Biotechnology 34, 999–1001 (2016) | doi:10.1038/nbt1016-999
Published online 11 October 2016
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Early clinical data raise the bar for hemophilia gene therapies
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A gene therapy approach has the potential to obviate the need for regular intravenous injections of bioengineered coagulation factor VIII (pictured) to prevent bleeds in patients with severe hemophilia A.
Several gene therapy companies reported promising early clinical data in July showing that they could restore healthy blood clotting factor levels in people with severe hemophilia. BioMarin Pharmaceutical presented interim results from a phase 1/2 trial in patients with hemophilia A at the World Federation of Hemophilia 2016 World Congress, demonstrating its gene therapy could increase factor VIII activity levels to at least 10% of normal in all seven subjects who received the highest dose, with two patients producing more than double the normal levels several months after
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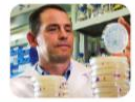

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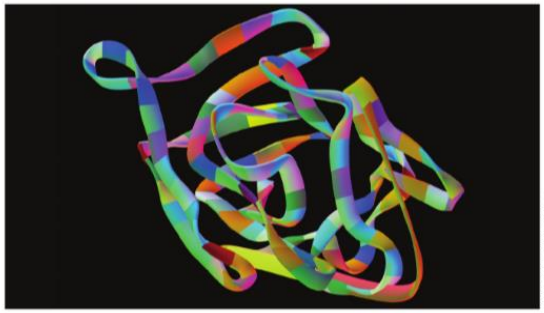
Early clinical data raise the bar for hemophilia gene therapies

Several gene therapy companies reported promising early clinical data in July showing that they could restore healthy blood clotting factor levels in people with severe hemophilia. BioMarin Pharmaceutical presented interim results from a phase 1/2 trial in patients with hemophilia A at the World Federation of Hemophilia 2016 World Congress, demonstrating its gene therapy could increase factor VIII activity levels to at least 10% of normal in all seven subjects who received the highest dose, with two patients producing more than double the normal levels several months after treatment. Spark Therapeutics and uniQure also provided encouraging updates from their own phase 1/2 trials for gene therapies for hemophilia B at the same Orlando meeting.

"We raised the bar," says Barrie Carter, head of vector biology at BioMarin. Before these trials, the expectation was that gene therapies might elevate clotting factor levels enough to transform severe hemophilia into a moderate or mild (~10% of normal) form of the disease. Now, it seems it may be possible to restore patients' natural clotting to eliminate the disease altogether—and, in fact, at the upper activity levels observed in the BioMarin trial the worry shifts from uncontrolled bleeding episodes to excessive clotting in the blood vessels. "It's a nice problem to have," says Amit Nathwani, a hematologist at the University College London (UCL), who did much of the preclinical work on the gene therapy before licensing the product to the San Rafael, California–based BioMarin.

Some onlookers, however, warn against jumping to conclusions based on initial find-

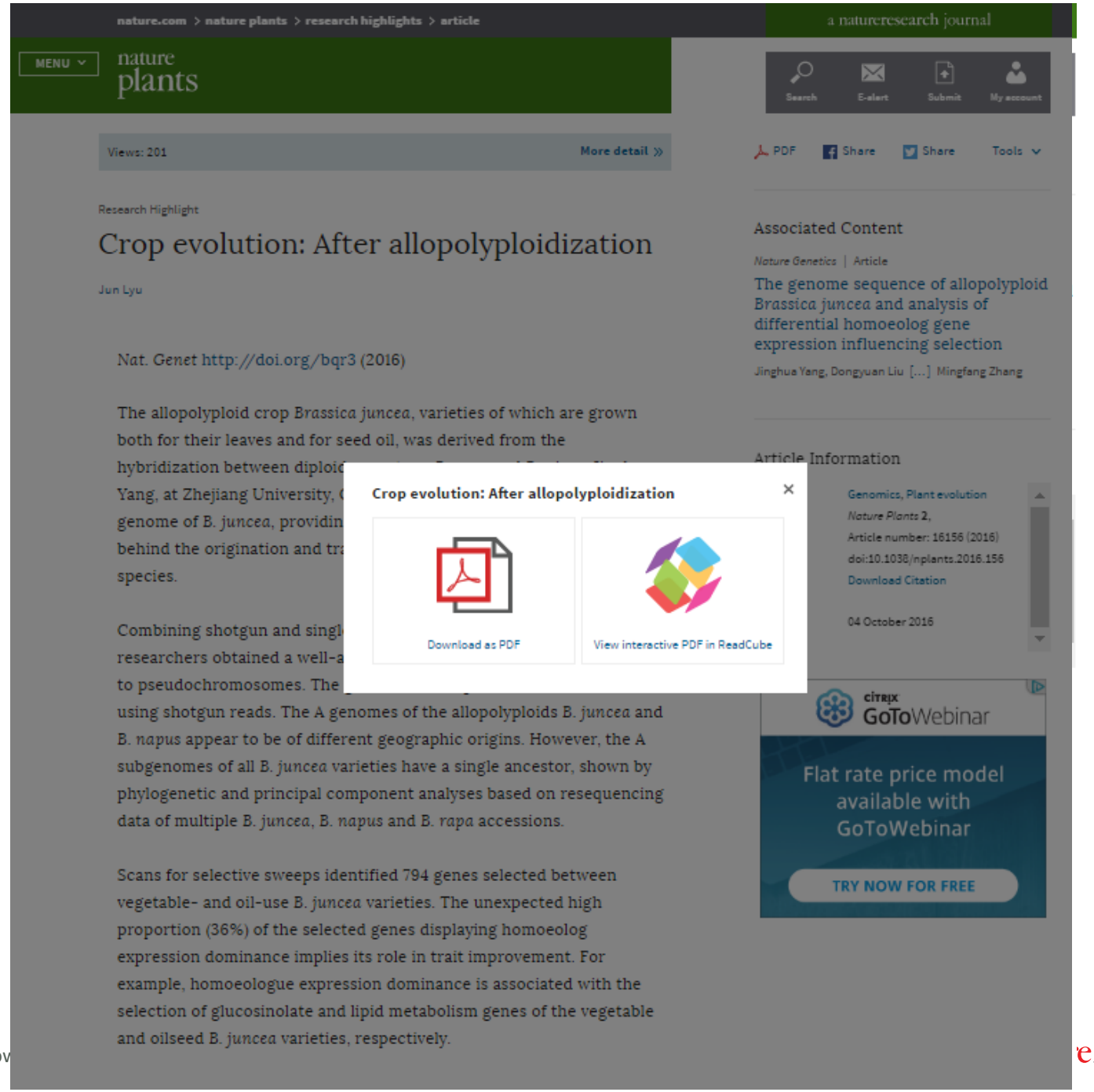


Alfred Pasieka / Science Source

A gene therapy approach has the potential to obviate the need for regular intravenous injections of bioengineered coagulation factor VIII (pictured) to prevent bleeds in patients with severe hemophilia A.

linked condition) compared with the 125,000 afflicted by hemophilia A—scientists considered the genetic deficiency in hemophilia B more straightforward to tackle. This is because the gene coding for factor IX is smaller and easier to insert into many viral vectors with robust expression than the factor VIII gene mutated in hemophilia A.

But early trials of gene therapies in hemophilia B between 1998 and 2001 yielded modest and temporary benefits for patients, with some major safety concerns. The first real success came only in 2010 when a team led by Nathwani and Andrew Davidoff from the St. Jude Children's Research Hospital in Memphis, the response to two months because most recipients had pre-existing neutralizing antibodies to the virus. To overcome the immunity hurdle, the St. Jude–UCL collaborators placed the AAV2 sequences in a capsid from the less prevalent AAV8 strain. A single intravenous infusion of this vector restored factor IX expression in patients to sustained levels in the range of 1–6% of normal values with no toxic effects after three years, on average (*N. Engl. J. Med.* **371**,1994–2004, 2014). At the highest dose, four out of six patients initially experienced a transient increase in liver transaminase levels, a marker of liver damage, but this was managed successfully with cortico-



Research Highlight

Crop evolution: After allopolyploidization

Jun Lyu

Nat. Genet http://doi.org/bqr3 (2016)

The allopolyploid crop *Brassica juncea*, varieties of which are grown both for their leaves and for seed oil, was derived from the hybridization between diploid

Yang, at Zhejiang University,

genome of *B. juncea*, providin

behind the origination and tra

species.

Combining shotgun and singl

researchers obtained a well-a

to pseudochromosomes. The

using shotgun reads. The A genomes of the allopolyploids *B. juncea* and *B. napus* appear to be of different geographic origins. However, the A subgenomes of all *B. juncea* varieties have a single ancestor, shown by phylogenetic and principal component analyses based on resequencing data of multiple *B. juncea*, *B. napus* and *B. rapa* accessions.

Scans for selective sweeps identified 794 genes selected between vegetable- and oil-use *B. juncea* varieties. The unexpected high proportion (36%) of the selected genes displaying homoeolog expression dominance implies its role in trait improvement. For example, homoeologue expression dominance is associated with the selection of glucosinolate and lipid metabolism genes of the vegetable and oilseed *B. juncea* varieties, respectively.

Associated Content

Nature Genetics | Article

The genome sequence of allopolyploid *Brassica juncea* and analysis of differential homoeolog gene expression influencing selection

Jinghua Yang, Dongyuan Liu [...] Mingfang Zhang

Article Information

Genomics, Plant evolution

Nature Plants 2,

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doi:10.1038/nplants.2016.156

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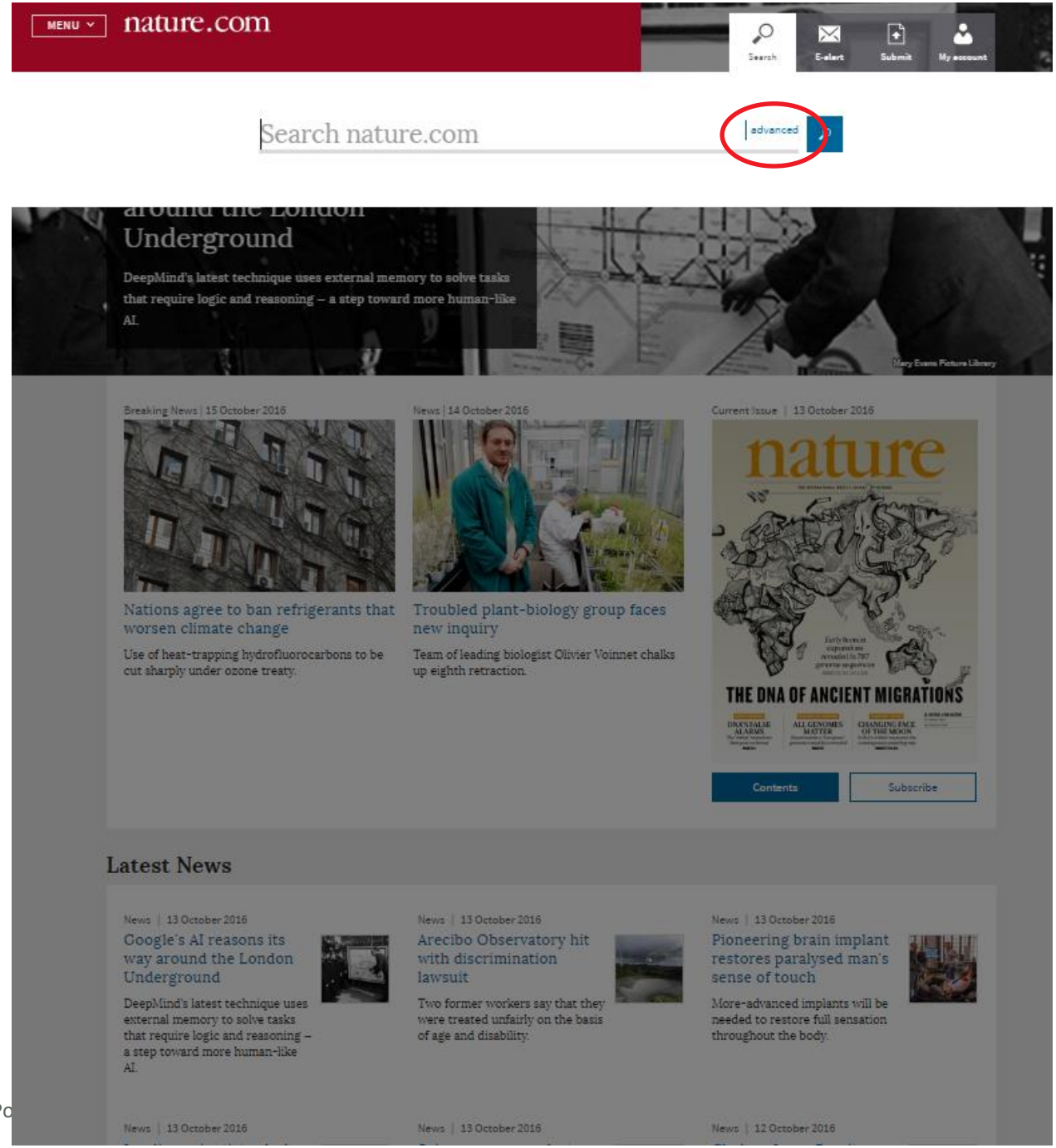
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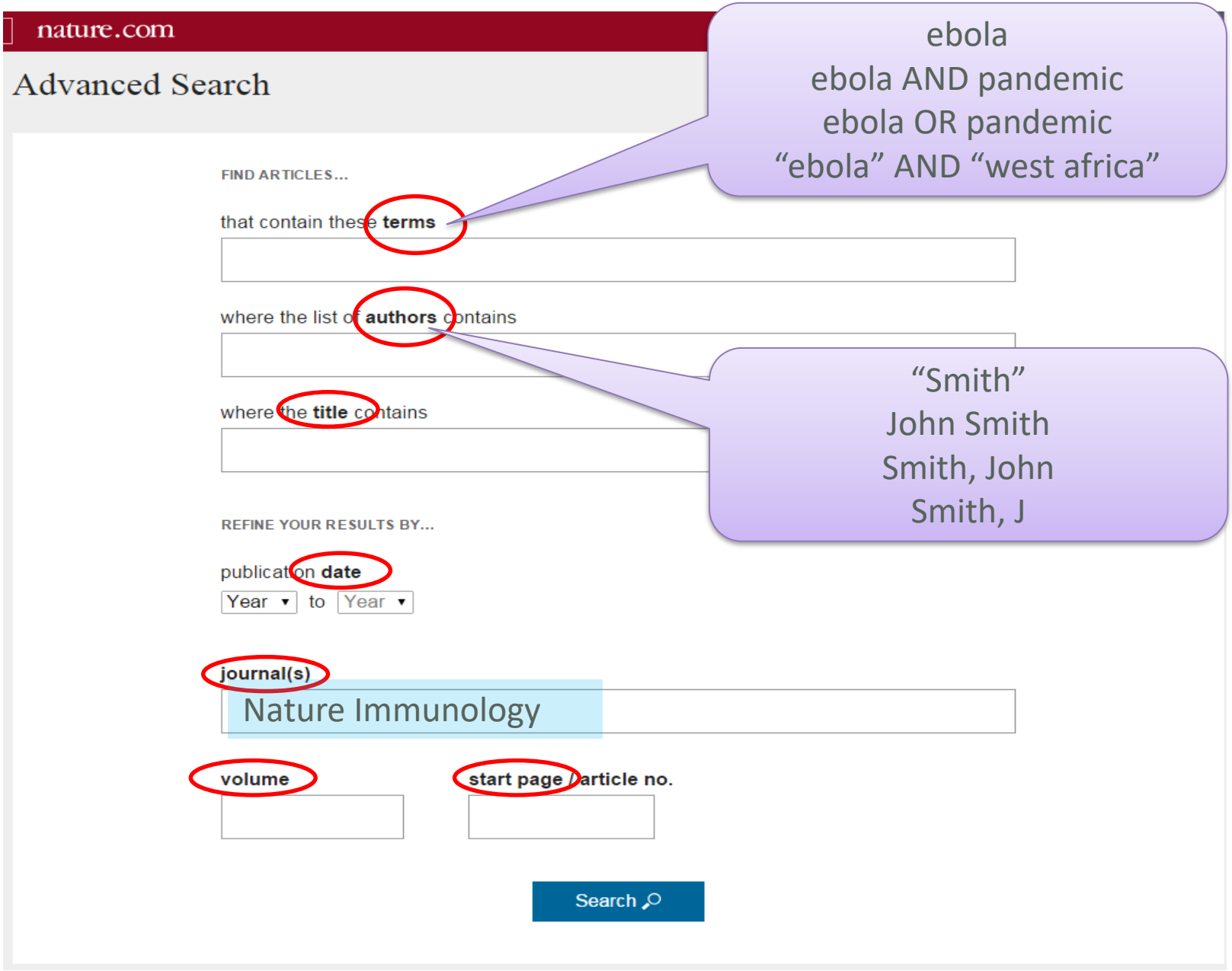
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Article altmetrics

A quick overview of Altmetrics

- Altmetric score = automated algorithm.
- Represents weighted count of the attention given to an article.
- Weighted to reflect the relative reach of each type of source.
- I.e. the average newspaper story is more likely to bring attention to the research output than the average tweet.

**Adapted from www.support.altmetric.com*

News	8
Blogs	5
Twitter	1
Facebook	0.25
Sina Weibo	1
Wikipedia	3
Policy Documents (per source)	3
Q&A	0.25
F1000/Publons/Pubpeer	1
YouTube	0.25
Reddit/Pinterest	0.25
LinkedIn	0.5

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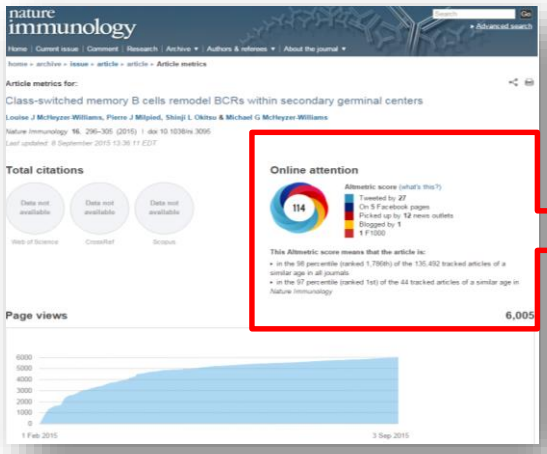

Online attention

Altmetric score (what's this?)

- Tweeted by **27**
- On **5** Facebook pages
- Picked up by **12** news outlets
- Blogged by **1**
- **1** F1000

This Altmetric score means that the article is:

- in the 98 percentile (ranked 1,786th) of the 135,492 tracked articles of a similar age in all journals
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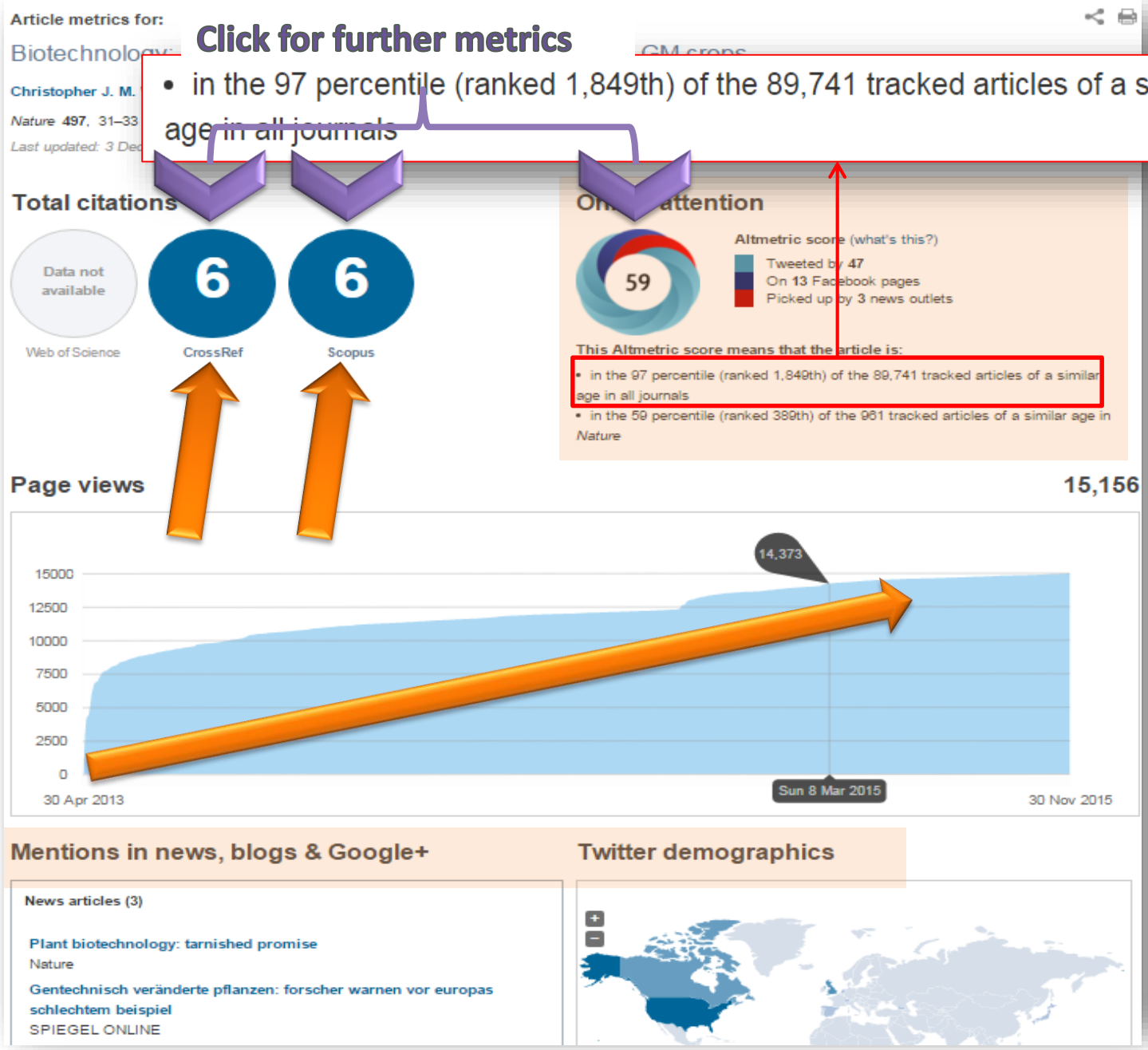
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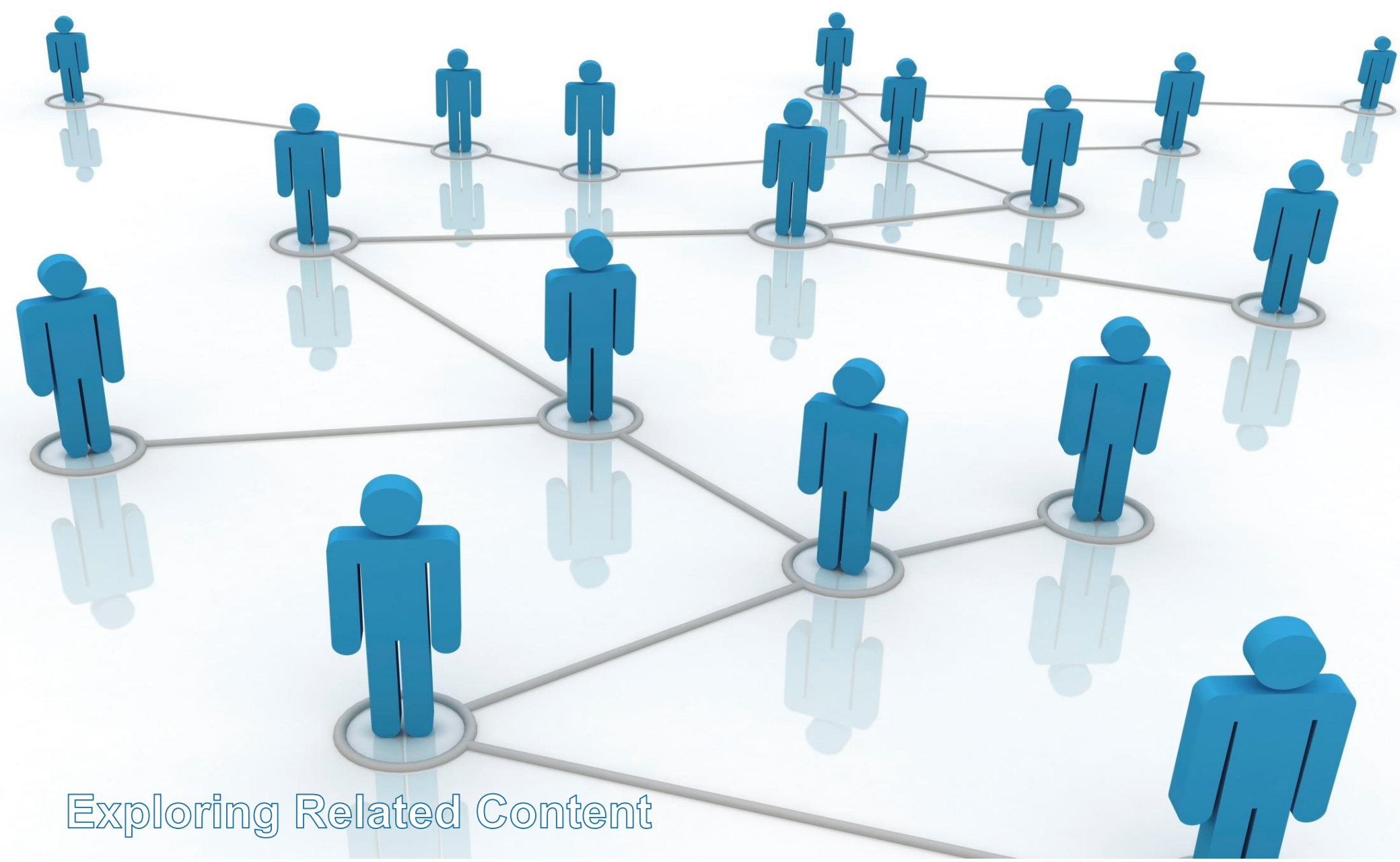
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Simon Bélanger & Shane Crotty

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Thomas Dörner & Peter E. Lipsky

Nature Reviews Rheumatology

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