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Cambridge & Chelmsford

Ljubljana, 12th September 2012

# Scientific integrity: can Molecular Medicine be trusted?

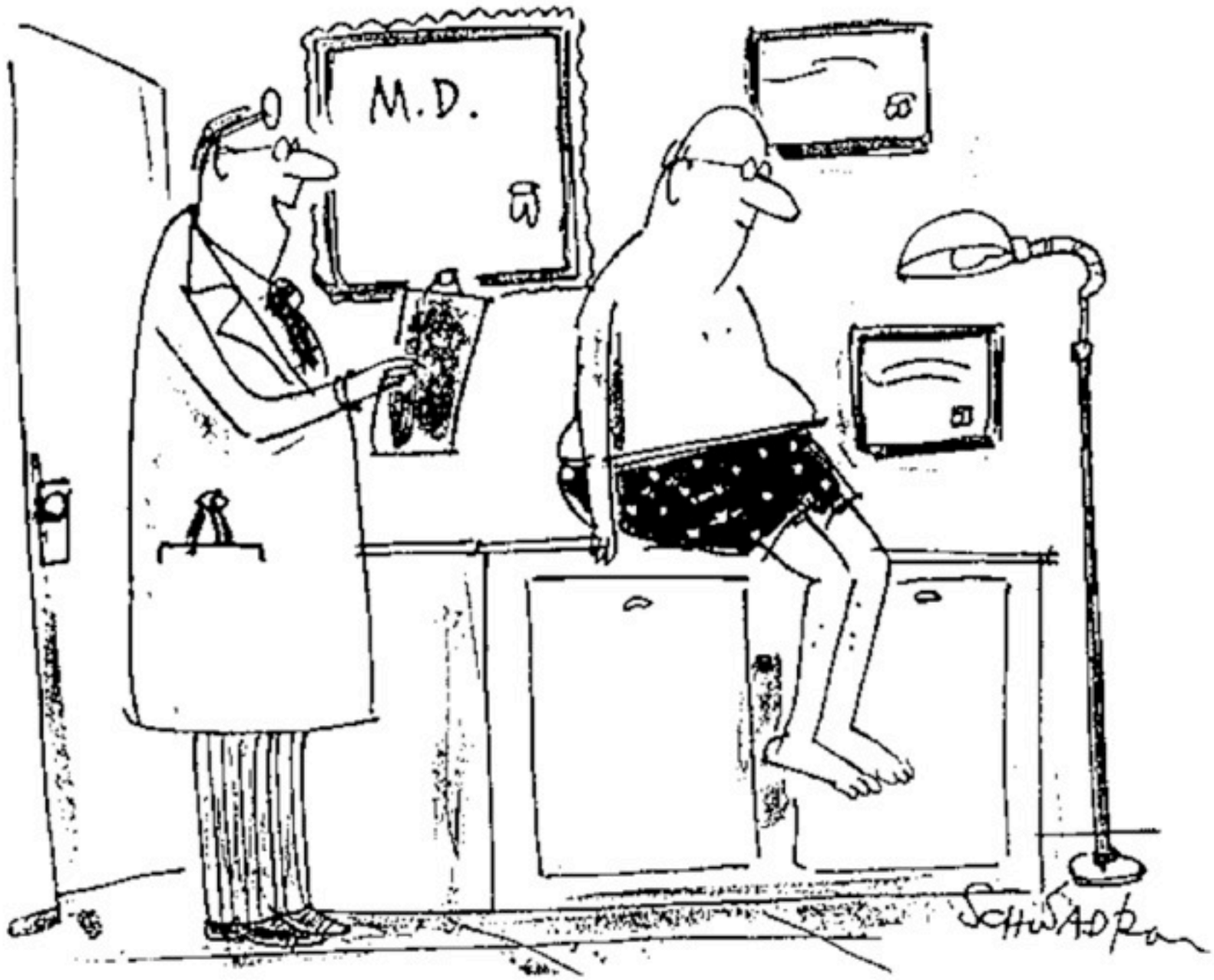
Stephen Bustin BA(Mod) PhD FSB
Professor of Allied Health and Medicine

Anglia Ruskin University

# Aim

- To demonstrate that advances in molecular medicine need to be treated with caution

"Good news Mr. Jones, while your cholesterol hasn't changed, the research has!"



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Clin Transl Oncol (2011) 13:419-425
DOI 10.1007/s12094-011-0676-z

RESEARCH ARTICLES

# Gene expression signature and response to the use of leucovorin, fluorouracil and oxaliplatin in colorectal cancer patients

**Toshiaki Watanabe · Takashi Kobunai · Yoko Yamamoto · Keiji Matsuda · Soichiro Ishihara · Keijiro Nozawa · Hisae Iinuma · Tsuyoshi Konishi · Hisanaga Horie · Hiroki Ikeuchi · Kiyoshi Eshima · Tetsuichiro Muto**

**British Journal of Cancer (2012) 106,** 126 – 132
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**www.bjcancer.com**

# Potential responders to FOLFOX therapy for colorectal cancer by Random Forests analysis

**S Tsuji[1], Y Midorikawa[1,2,3], T Takahashi[4], K Yagi[1], T Takayama[3], K Yoshida[4], Y Sugiyama*[,2] and H Aburatani[1]**

*[1]Genome Science Division, Research Center for Advanced Science and Technology, The University of Tokyo, Tokyo, Japan; [2]Department of Surgery, Teikyo University School of Medicine University Hospital, Mizonokuchi, Kawasaki, Japan; [3]Department of Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan; [4]Department of Oncologic Surgery, Gifu University, Gifu, Japan*

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**Table 2** The 27-probe signature that predicts response to FOLFOX

| Identifier | Gene Symbol | Description | ag-P ll | Flag-M call |
|---|---|---|---|---|
| 232122_s_at | VEPH1 | Ventricular zone expressed PH domain homolo | 5 | 0 |
| 211494_s_at | SLC4A4 | Solute carrier family 4, sodium bicarbonate co | 3 | 1 |
| 210619_s_at | HYAL1 | Hyaluronoglucosaminidase 1 | 5 | 0 |
| 215164_at | | Transcribed locus | 4 | 0 |
| 1558549_s_at | VNN1 | Vanin 1 | | 0 |
| 235777_at | ANKRD44 | Ankyrin repeat domain 44 | 4 | 3 |
| 1552797_s_at | PROM2 | Prominin 2 | 7 | 0 |
| 226281_at | DNER | Delta/notch-like EGF repeat containing | 0 | 2 |
| 1554027_a_at | SLC4A4 | Solute carrier family 4, sodium bicarbonate co | 4 | 0 |
| 1559975_at | BTG1 | B-cell translocation gene 1, anti-proliferative | 0 | 2 |
| 243761_at | PFTK1 | PFTAIRE protein kinase 1 /// similar to rCG41 | 4 | 1 |
| 226211_at | MEG3 | Maternally expressed 3 | 3 | 1 |
| 205715_at | BST1 | Bone marrow stromal cell antigen 1 | 5 | 1 |
| 1552912_a_at | IL23R | Interleukin 23 receptor | 2 | 1 |
| 242033_at | RNF180 | Ring finger protein 180 | 3 | 3 |
| 232330_at | C7orf44 | Chromosome 7 open reading frame 44 | 0 | 2 |
| 206525_at | GABRR1 | Gamma-aminobutyric acid (GABA) receptor, r | 4 | 3 |
| 1566551_at | | MRNA; cDNA DKFZp586L2217 (from clone | 7 | 1 |
| 208126_s_at | CYP2C18 | Cytochrome P450, family 2, subfamily C, poly | 2 | 1 |
| 204942_s_at | ALDH3B2 | Aldehyde dehydrogenase 3 family, member B2 | 3 | 3 |
| 235831_at | | Transcribed locus | 3 | 1 |
| 214308_s_at | HGD | Homogentisate 1,2-dioxygenase (homogentisa | 3 | 0 |
| 222934_s_at | CLEC4E | C-type lectin domain family 4, member E | 5 | 2 |
| 244441_at | | Transcribed locus | 5 | 0 |
| 235209_at | RPESP | RPE-spondin | 0 | 0 |
| 235104_at | ERAP2 | Endoplasmic reticulum aminopeptidase 2 | 5 | 0 |
| 219759_at | ERAP2 | Endoplasmic reticulum aminopeptidase 2 | 4 | 1 |



**Table 2** Top 50 classifier genes after exclusion of outliers

| Probe set ID | Gene symbol |
|---|---|
| 227489_at | SMURF2 |
| 226797_at | MBTD1 |
| 203410_at | AP3M2 |
| 226106_at | RNF141 |
| 214101_s_at | NPEPPS |
| 231953_at | BPTF |
| 201455_s_at | NPEPPS |
| 235125_x_at | FAM73A |
| 202630_at | APPBP2 |
| 223443_s_at | AMZ2P1 |
| 1555875_at | SRGAP1 |
| 201158_at | NMT1 |
| 227105_at | CSPP1 |
| 217672_x_at | EIF1 |
| 205250_s_at | CEP290 |
| 202880_s_at | CYTH1 |
| 1552283_s_at | ZDHHC11 |
| 225384_at | DOCK7 |
| 202034_x_at | RB1CC1 |
| 222715_s_at | SYNRG |
| 226441_at | MAP3K2 |
| 240304_s_at | **TMC5** |
| 200090_at | FNTA |
| 53071_s_at | C17orf101 |
| 212561_at | DENND5A |
| 200811_at | CIRBP |
| 206600_s_at | SLC16A5 |
| 227064_at | ANKRD40 |
| 205596_s_at | SMURF2 |
| 230211_at | – |
| 203651_at | ZFYVE16 |
| 226580_at | BRMS1L |
| 222589_at | NLK |
| 227564_at | HGSNAT |
| 64418_at | SYNRG |
| 223595_at | TMEM133 |
| 230621_at | IAH1 |
| 225572_at | CREB1 |
| 225198_at | VAPA |
| 202460_s_at | LPIN2 |
| 212704_at | ZCCHC11 |
| 204485_s_at | TOM1L1 |
| 212397_at | RDX |
| 225595_at | CREBZF |
| 202814_s_at | HEXIM1 |
| 204208_at | RNGTT |
| 222656_at | UBE2W |
| 203116_s_at | FECH |
| 227395_at | FLJ38498 |
| 201454_s_at | NPEPPS |

Bold entry: down-regulated genes in non-responders.

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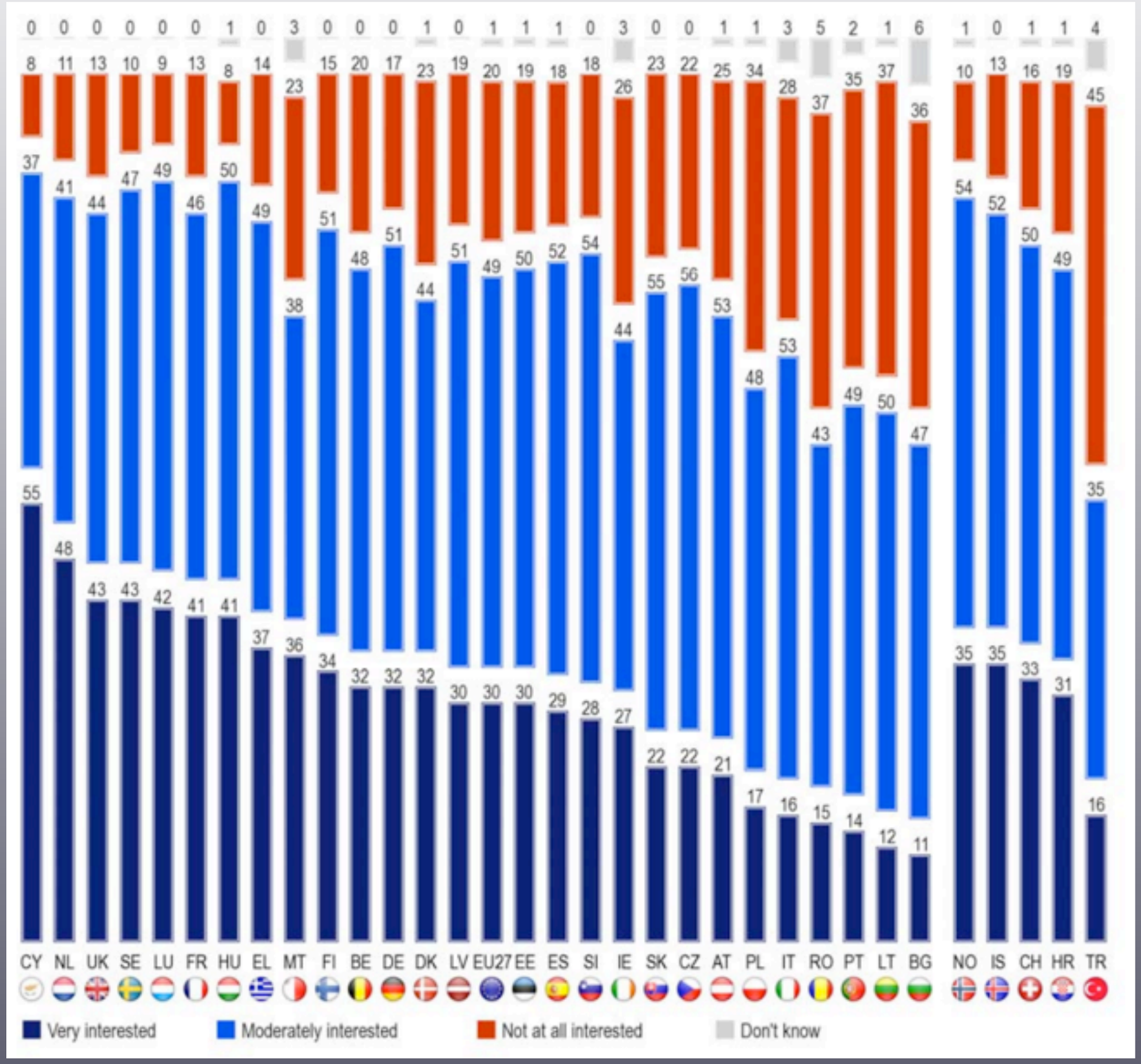
van de Vijver MJ, He YD, van't Veer LJ, Dai H, Hart AA, Voskuil DW, Schreiber GJ, Peterse JL, Roberts C, Marton MJ, Parrish M, Atsma D, Witteveen A, Glas A, Delahaye L, van der Velde T, Bartelink H, Rodenhuis S, Rutgers ET, Friend SH, Bernards R (2002) A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med* **347:** 1999 – 2009

Wu B, Abbott T, Fishman D, McMurray W, Mor G, Stone K, Ward D, Williams K, Zhao H (2003) Comparison of statistical methods for classification of ovarian cancer using mass spectrometry data. *Bioinformatics* **19:** 1636 – 1643

# Interest in science




Science and Technology: A special Eurobarometer public survey (2010)

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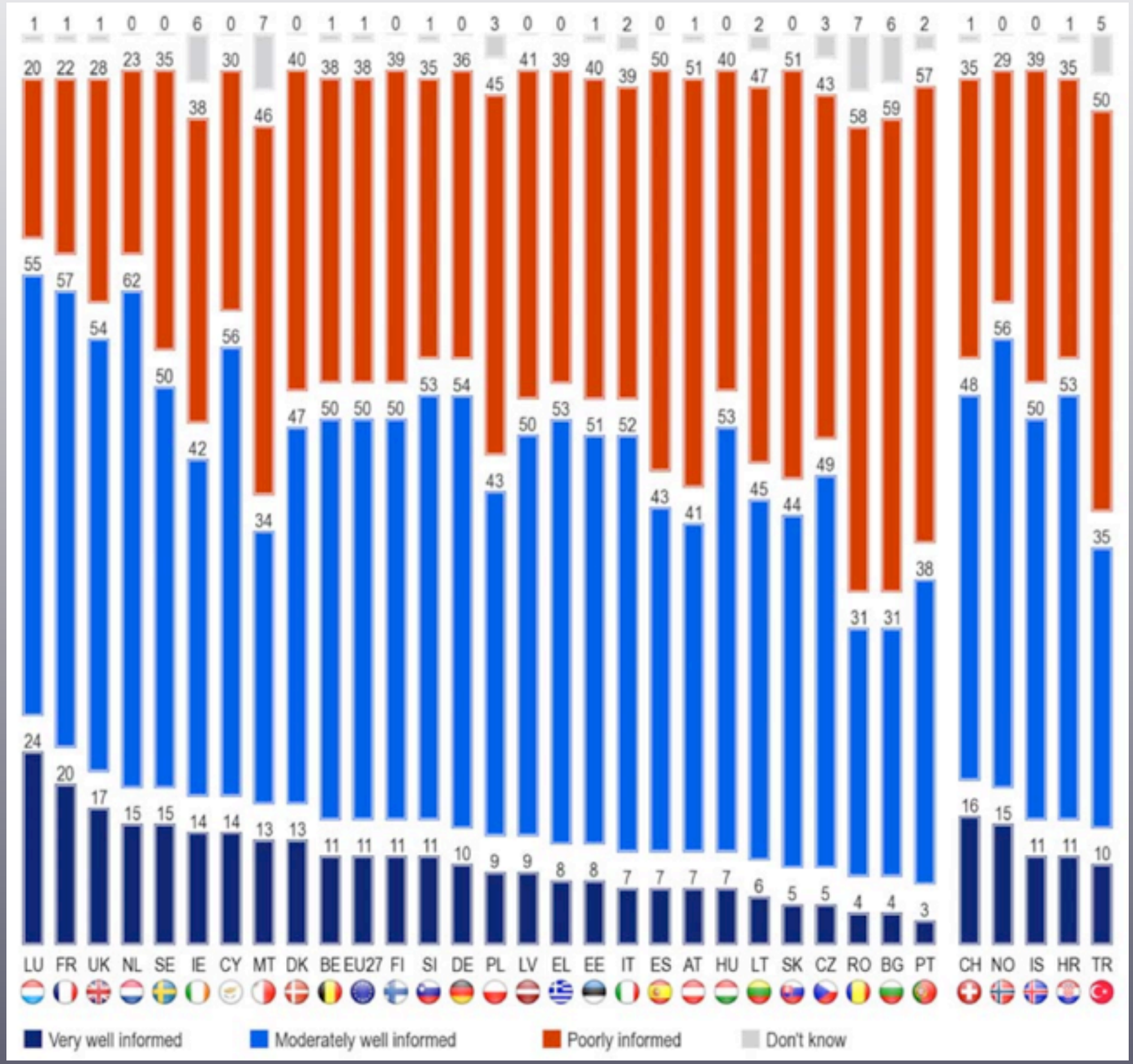
# Knowledge of science




Science and Technology: A special Eurobarometer public survey (2010)

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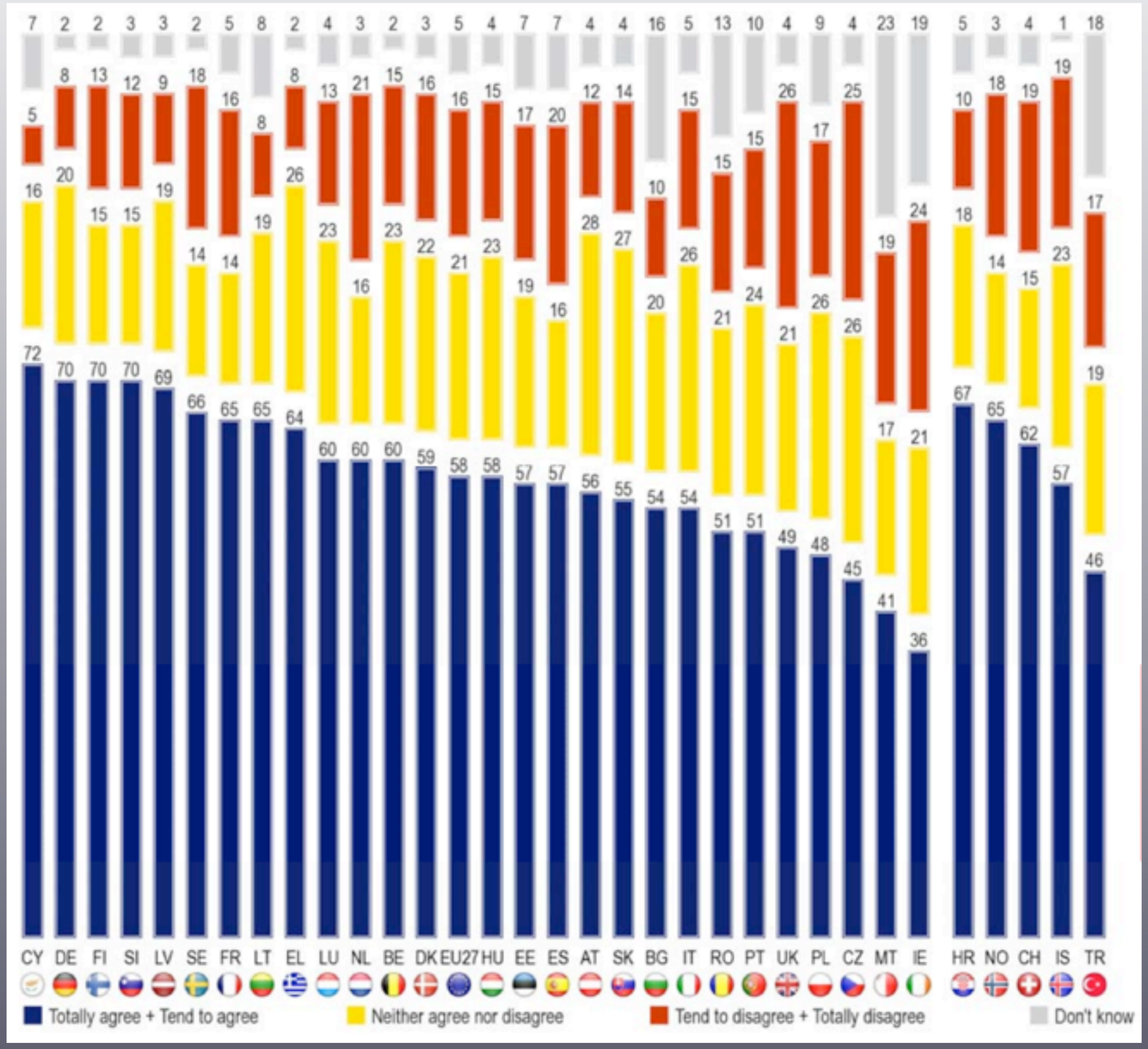
# Scientists are not truthful




Science and Technology: A special Eurobarometer public survey (2010)

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# The Hidden Research Paper

Richard Horton, FRCP

**Context** To determine whether the views expressed in a research paper are accurate representations of contributors' opinions about the research being reported.

**Methods** Purposive sampling of 10 research articles published in *The Lancet*; qualitative analysis of answers to 6 questions about the meaning of the study put to contributors who were listed on the byline of these articles. Fifty-four contributors listed on the bylines of the 10 articles were evaluated, and answers to questions were compared between contributors within research groups and against the published research report.

**Results** A total of 36 (67%) of 54 contributors replied to this survey. Important weaknesses were often admitted on direct questioning but were not included in the published article. Contributors frequently disagreed about the importance of their findings, implications, and directions for future research. I could find no effort to study systematically past evidence relating to the investigators' own findings in either survey responses or the published article. Overall, the diversity of contributor opinion was commonly excluded from the published report. I found that discussion sections were haphazardly organized and did not deal systematically with important questions about the study.

**Conclusions** A research paper rarely represents the opinions of those scientists whose work it reports. The findings described herein reveal evidence of (self-)censored criticism, obscured meanings, confused assessment of implications, and failures to indicate directions for future research. There is now empirical support for the introduction of structured discussion sections in research papers. Editors might also explore ways to recover the plurality of contributors' opinions.

WHAT HAPPENS WHEN SCIentists disagree? Most times, readers of research papers never know. However, in 1995, a dispute among the writing committee of the Italian Multicentre Acute Stroke Trial spilled out onto the pages of *The Lancet*.[1,2] During peer review, it became clear that 2 committee members interpreted the results of the trial very differently from their colleagues. They had, for the good of the collaboration, self-censored their own views. How-

original article appeared.[4] Harmony among authors cannot be relied on.

A crisis over definitions of authorship during recent years has led several medical journals to discard rigid rules for who can or who cannot be an author. Instead, the idea of the contributor has emerged.[5] In place of the assumption that scientists named on the byline of an article are true authors, journals such as *The Lancet*, *BMJ*, and *Annals of Internal Medicine* now require contributors to state explicitly what part they played in the research being reported. This conceptual shift was best summarized by Rennie et al[5]: "Contribution is the activity of sci-

does not take account of the ideas or interpretations contributed to the research being reported. I wanted to know whether the views expressed in a research paper are accurate representations of contributors' opinions.

## METHODS

I selected 10 articles published in *The Lancet* during 2000 (TABLE). This study had a qualitative design: articles were selected purposively with varying numbers of contributors, across a range of subject areas, and including a spectrum of research methods. I wrote to the corresponding author of each research article to secure permission to

phoned once to obtain replies.

Once available replies had been collected, individual answers to questions were compared with one another among contributors for each research paper. These answers were also compared with the contents of the published article. Finally, contributor sections were examined to discover if there were any identifiable connections between stated contributions and the answers to these 6 questions.

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Essay

# Why Most Published Research Findings Are False

John P. A. Ioannidis


## Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these problems for the conduct and interpretation of research.


Published research findings are sometimes refuted by subsequent evidence, with ensuing confusion and disappointment. Refutation and controversy is seen across the range of research designs, from clinical trials and traditional epidemiological studies [1–3] to the most modern molecular research [4,5]. There is increasing concern that in modern research, false findings may be the majority or even the vast majority of published research claims [6–8]. However, this should not be surprising. It can be proven that most claimed research findings are false. Here I will examine the key factors that influence this problem and some corollaries thereof.

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.

### Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a *p*-value less than 0.05. Research is not most appropriately represented and summarized by *p*-values, but, unfortunately, there is a widespread notion that medical research articles

**It can be proven that most claimed research findings are false.**

should be interpreted based only on *p*-values. Research findings are defined here as any relationship reaching formal statistical significance, e.g., effective interventions, informative predictors, risk factors, or associations. "Negative" research is also very useful. "Negative" is actually a misnomer, and the misinterpretation is widespread. However, here we will target relationships that investigators claim exist, rather than null findings.

As has been shown previously, the probability that a research finding is indeed true depends on the prior probability of it being true (before doing the study), the statistical power of the study, and the level of statistical significance [10,11]. Consider a 2 × 2 table in which research findings are compared against the gold standard of true relationships in a scientific field. In a research field both true and false hypotheses can be made about the presence of relationships. Let $R$ be the ratio of the number of "true relationships" to "no relationships" among those tested in the field. $R$ is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R + 1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, $\alpha$. Assuming that $c$ relationships are being probed in the field, the expected values of the 2 × 2 table are given in Table 1. After a research finding has been claimed based on achieving formal statistical significance, the post-study probability that it is true is the positive predictive value, PPV. The PPV is also the complementary probability of what Wacholder et al. have called the false positive report probability [10]. According to the 2 × 2 table, one gets $PPV = (1 - \beta)R/(R - \beta R + \alpha)$. A research finding is thus

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**Abbreviation:** PPV, positive predictive value

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**Competing Interests:** The author has declared that no competing interests exist.

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OPINION

# Modern biomedical research: an internally self-consistent universe with little contact with medical reality?

*David F. Horrobin*

Congruence between *in vitro* and animal models of disease and the corresponding human condition is a fundamental assumption of much biomedical research, but it is one that is rarely critically assessed. In the absence of such critical assessment, the assumption of congruence may be invalid for most models. Much more open discussion of this issue is required if biomedical research is to be clinically productive.

Pharmaceutical research is failing in its ability to deliver new drugs. Furthermore, as much pharmaceutical research draws on the wider biomedical research community, the possibility is that biomedical research in general is also failing. There can be no doubt about the reality of the pharmaceutical failure. Almost all the major drug companies are generating inadequate numbers of new drugs and as a result their market values have fallen catastrophically. There is no relief in sight. The US FDA and the European Medicines Evaluation Agency (EMEA) have recently announced that 2002 applications for new drug approvals are well below the depressingly low levels of 2001. What is going on?

The failure is certainly not due to lack of investment, as the major drug companies are spending well over $30 billion per year on R&D. Two other explanations are common. One is that all the easy problems have been solved: what is left is much more difficult. The other is that the new technologies will bear fruit in time given enough further investment. There is, of course, no way to critically evaluate these two alternatives: all we can do is hope.

A fourth possibility does deserve critical evaluation, but attracts surprisingly little open discussion. This is that biomedical science, and hence pharmaceutical science, has taken a wrong turn in its relationship to human disease. This discussion paper raises some issues which have been swept under the carpet by the pharmaceutical and medical research communities.

## The glass bead game

A wonderful metaphor of much modern medical and pharmaceutical research can be found in the book entitled *The Glass Bead Game* by Herman Hesse[1] (FIG. 1). In this story, the leaders of the real world conspire with the brightest of scholars to create a magical state within a state, the isolated world of Castalia. Castalia recruits the most thoughtful and scholarly youths, educates them wonderfully well, and persuades them that the highest achievement of the human mind is to play the almost infinitely complicated and subtle 'glass bead game', an intellectual Olympics which challenges and stretches the most exceptional. The world of the game is beautifully refined and internally self-consistent. The only problems are that Castalia makes almost no contact with the real world, and that playing the game makes no contribution to real world issues. The outcome, however, is acceptable to all sides. The real world sidelines its potentially troublesome intellectuals by seducing them to play in their heavily subsidised glass cage. The intellectuals avoid the need to test their brains on any real issues.

When I look at the world of medical and pharmaceutical research it seems to me that we are well on the way to creating a Castalia which is entirely acceptable to the majority of its scientist-priests. They receive funding from the real world and are inducted into a complex organisation which, for those who know how to play the game, creates an ever-expanding universe of intellectual and social possibilities. This universe, like Hesse's Castalia, has few points of interaction with real medical problems: its inhabitants, like the original Castalians, are happy to keep it that way. The difference from Castalia is that, with medical research, the real world providing the funding does in the end expect the medical Castalia to provide a pay off. While Hesse's Castalians were confident of the absence of any need to justify their game, the medical Castalians are aware that their funding is to some degree conditional. So the latter constantly make announcements that exaggerate the importance for medicine of some trivial laboratory finding, and constantly assert that if only the public or the pharmaceutical industry will continue to supply money then success will be assured.

I am increasingly fearful that much of the hyped promise is illusory. Most medical and pharmaceutical research is now of one of three broad types, which are informed by a fourth — the molecular biology of the genome. The other three types of research are cell culture, traditional animal models of disease (such as hypertension, arthritis, cancer or multiple sclerosis), and the new mouse models involving various types of gene knockouts, knock-ins and their variants, which are currently threatening to overwhelm animal facilities worldwide. We are repeatedly told by the high priests of the medical Castalia that these amazing cascades of new knowledge will in the not-too-distant

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# Research publication

- Transmission of new information to the scientific community

Vol 449|25 October 2007|**doi:10.1038/nature06196**

nature

ARTICLES

# Identification of stem cells in small intestine and colon by marker gene *Lgr5*

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HARVARD UNIVERSITY

MRC Medical Research Council

Department of Health & Human Services National Institutes of Health The Nation's Medical Research Agency

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Journal Summary List

Journal Title Change

Journals from: subject categories OBSTETRICS & GYNECOLOGY VIEW CATEGORY SUMMARY LIST

Sorted by: Impact Factor SORT AGAIN

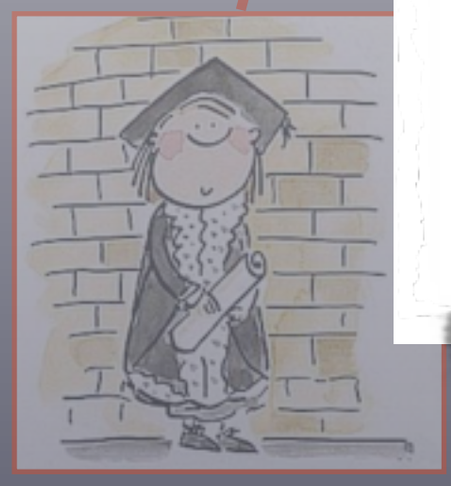
Change sort to impact factor (from title)

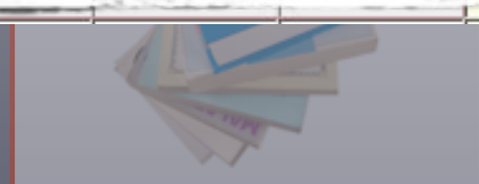
Journals 1 - 20 (of 59) [ 1 | 2 | 3 ] Page 1 of 3

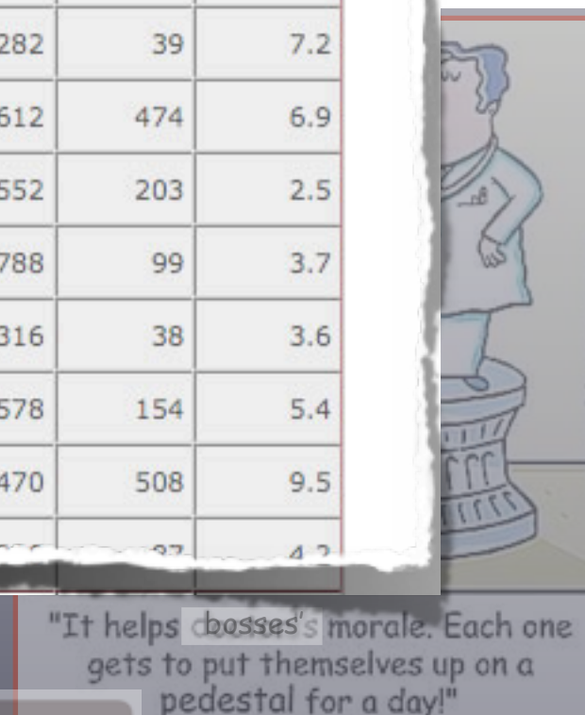
MARK ALL UPDATE MARKED LIST

*Ranking is based on your journal and sort selections.*

| Mark | Rank | Abbreviated Journal Title (linked to journal information) | ISSN | Total Cites | Impact Factor | Immediacy Index | Articles | Cited Half-life |
|---|---|---|---|---|---|---|---|---|
| ☐ | 1 | HUM REPROD UPDATE | 1355-4786 | 2658 | 6.793 | 1.069 | 58 | 5.1 |
| ☐ | 2 | OBSTET GYNECOL | 0029-7844 | 18473 | 3.813 | 1.452 | 186 | 8.7 |
| ☐ | 3 | HUM REPROD | 0268-1161 | 19772 | 3.769 | 0.734 | 477 | 6.2 |
| ☐ | 4 | OBSTET GYNECOL SURV | 0029-7828 | 1682 | 3.329 | 0.282 | 39 | 7.2 |
| ☐ | 5 | FERTIL STERIL | 0015-0282 | 18700 | 3.277 | 0.612 | 474 | 6.9 |
| ☐ | 6 | REPROD BIOMED ONLINE | 1472-6483 | 2124 | 3.206 | 0.552 | 203 | 2.5 |
| ☐ | 7 | MENOPAUSE | 1072-3714 | 1546 | 3.170 | 0.788 | 99 | 3.7 |
| ☐ | 8 | SEMIN REPROD MED | 1526-8004 | 550 | 3.000 | 0.316 | 38 | 3.6 |
| ☐ | 9 | PLACENTA | 0143-4004 | 3581 | 2.969 | 0.578 | 154 | 5.4 |
| ☐ | 10 | AM J OBSTET GYNECOL | 0002-9378 | 25749 | 2.805 | 0.470 | 508 | 9.5 |
| ☐ | 11 | J SOC GYNECOL INVEST | 1071-5576 | 1259 | 2.379 | [illegible] | [illegible] | 4.2 |








MRC Medical Research Council

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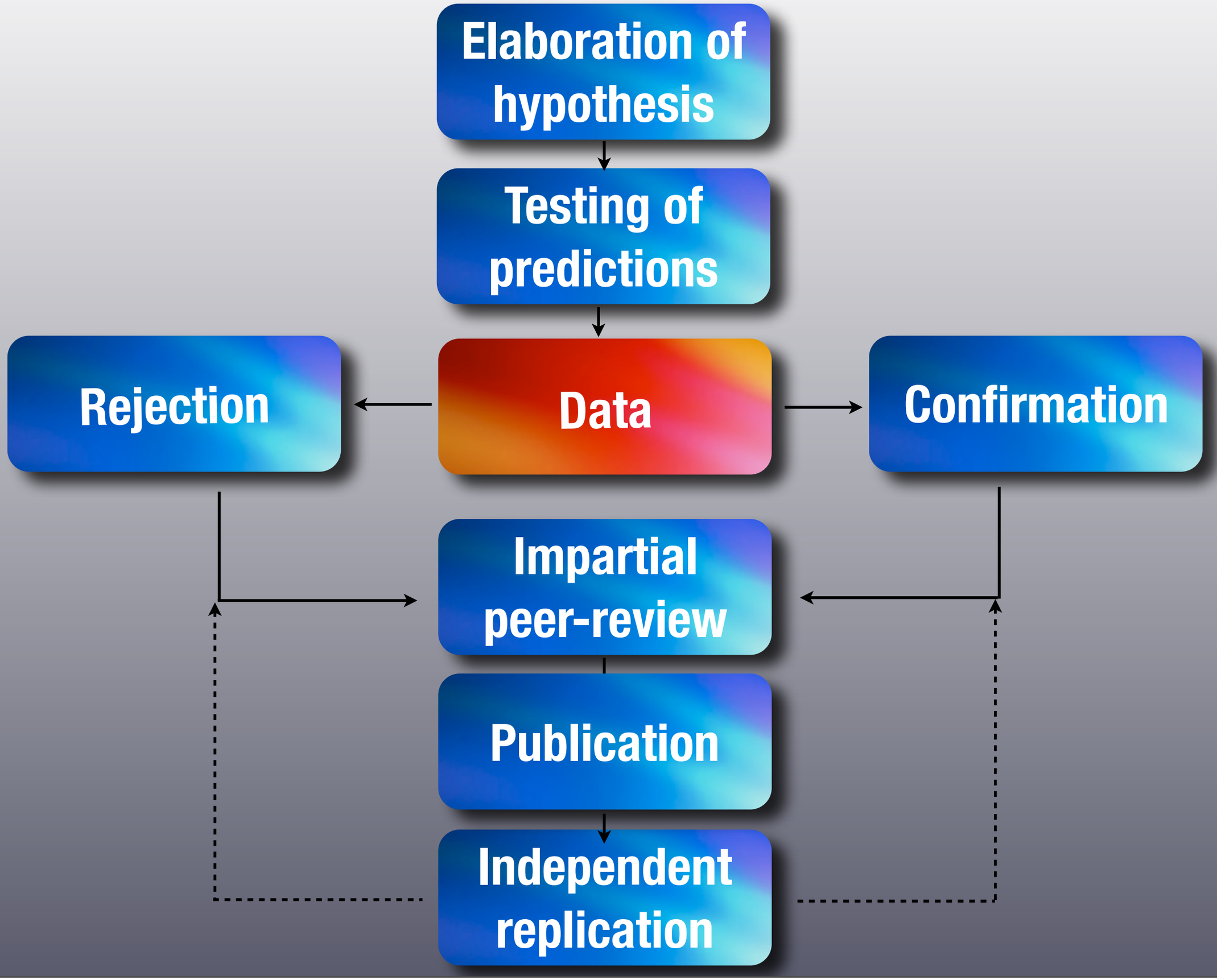

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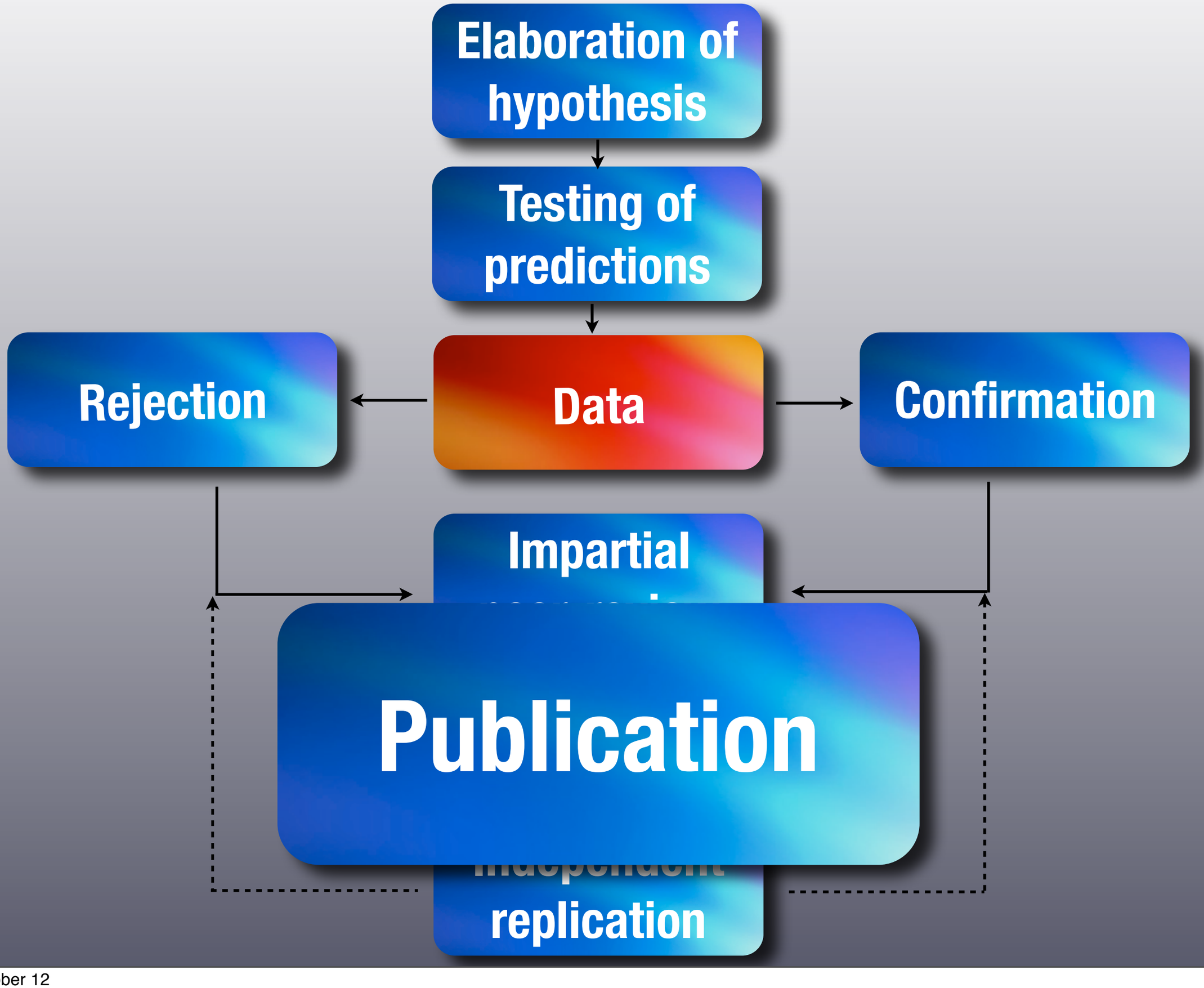

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Data

Elaboration of hypothesis

Testing of predictions

Rejection

Data

Confirmation

Impartial

Publication

independent

replication

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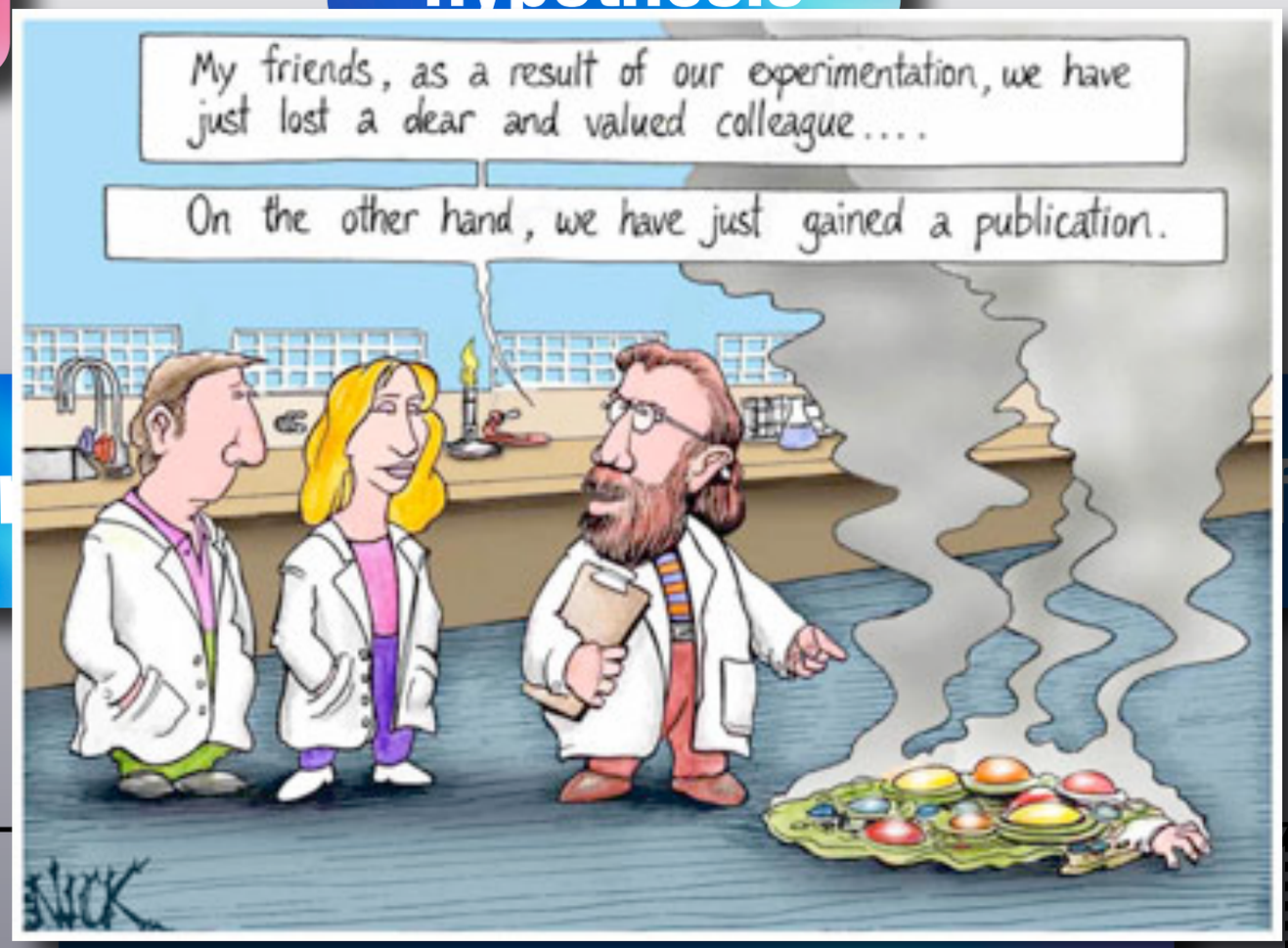
Data

Elaboration of hypothesis




Rejectio

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Publication

independent replication

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# MMR Controversy

Early report

1998

# Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

*A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith*

We have identified a chronic enterocolitis in children that may be related to neuropsychiatric dysfunction. In most cases, onset of symptoms was after measles, mumps, and rubella immunisation. Further investigations are needed to examine this syndrome and its possible relation to this vaccine.

We did not prove an association between measles, mumps, and rubella vaccine and the syndrome described. Virological studies are underway that may help to resolve this issue.

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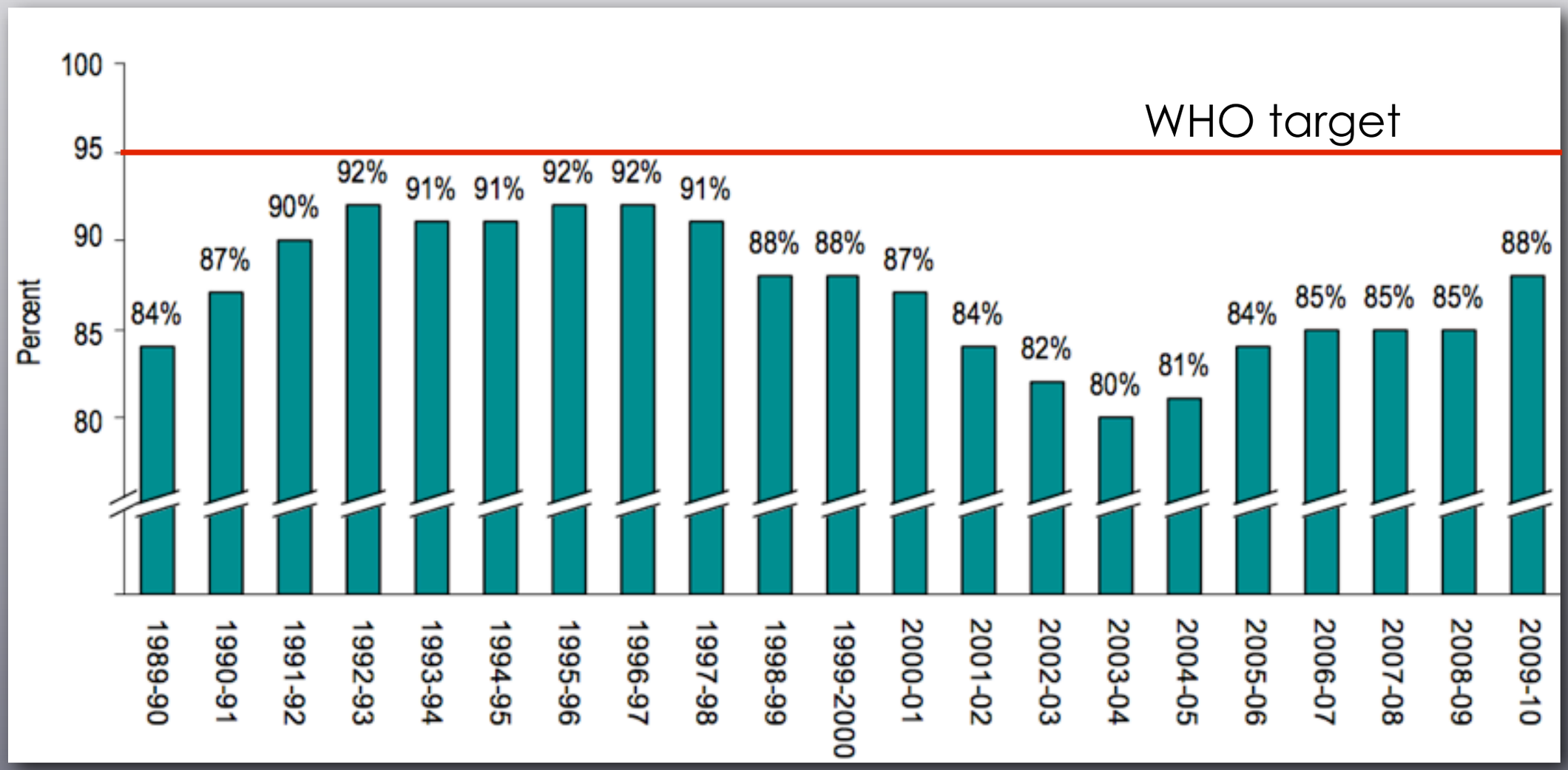
# MMR uptake




NHS Immunisation Statistics England 2009-10

# Former Government science chief: 'My MMR fears all coming true'

By Sue Corrigan

A FORMER Government medical officer responsible for deciding whether medicines are safe has accused the Government of "utterly inexplicable complacency" over the MMR triple vaccine for children.

Dr Peter Fletcher, who was Chief Scientific Officer at the Department of Health, said if it is proven that the jab causes autism, 'the refusal by governments to evaluate the risks properly will make this one of the greatest scandals in medical history'.

He added that after agreeing to be an expert witness on drug-safety trials for parents' lawyers, he had received and studied thousands of documents relating to the case which he believed the public had a right to see.

He said he has seen a 'steady accumulation of evidence' from scientists worldwide that the measles, mumps and rubella jab is causing brain damage in certain children.

PLEA: Elizabeth Smith is convinced the MMR jab caused Mark's condition and now faces prosecution over his truancy

'Our Mark had the jab. Now he lashes out – or hides under the table'

Daily Mail
WEDNESDAY, FEBRUARY 6, 2002
Newspaper of the Year 40p

LUCKY 7 PLAY TODAY ON PAGE 70

LYNDA LEE-POTTER

Hypocrisy and cant over MMR have done untold harm. Now we need the facts SEE PAGE 13

Research fuels fears as more outbreaks of measles emerge

# NEW ALERT ON MMR JAB

By Beezy Marsh and Jonathan Irwin

On Golden



The Mail on Sunday May 28, 2000

New study on controversial triple jab backs up the British doctor who caused a storm

# Now U.S. scientists say MMR could be linked with autism

By Sally Beck

NEW American research shows that there could be a link between the controversial MMR triple vaccine and autism and bowel disease in children.

The study appears to confirm the findings of British doctor Andrew Wakefield, who caused a storm in 1998 by suggesting a possible link.

Now a team from the Wake Forest University School of Medicine in North Carolina are examining 275 children with regressive autism and bowel disease – and of the 82 tested so far, 70 prove positive for the measles virus.

Last night the team's leader, Dr Stephen Walker, said: 'Of the handful of results we have in so far, all are vaccine strain and none are wild measles.

"This research proves that in the gastro-intestinal tract of a number of children who have been diagnosed with regressive autism, there is evidence of measles virus.

they have GI inflammation and other problems, it may be related to MMR.'

The 1998 study by Dr Wakefield, at the Royal Free Hospital in North London, and 12 other doctors claimed to have found a new bowel disease, autism enterocolitis.

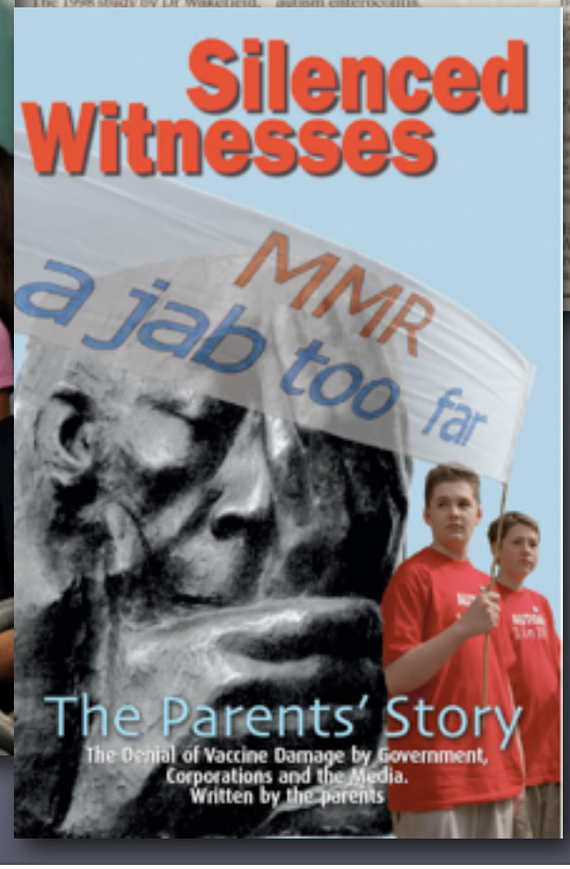
James's Hospital and Trinity College, Dublin, replicated his findings.

Last night Dr Wakefield said: 'This new study confirms what we found in British children and again with Professor O'Leary. The only exposure these children have had to measles is through the MMR vaccine.

'They were developing normally until they regressed. They now suffer autism and bowel disease.

'The Department of Health and some of the media wanted to dismiss our research as insignificant. The excuse was that no one else had the same findings as us. What they didn't say is that no one else had looked.'

A spokesman for the Department of Health said they had not read the American report, but added: 'MMR remains the best form of protection against measles, mumps and rubella.'



# News

## Measles once again endemic in the United Kingdom

**Editorial team (eurosurveillance@ecdc.europa.eu)**[1]
1. European Centre for Disease Prevention and Control, Stockholm, Sweden

Fourteen years after the local transmission of measles was halted in the United Kingdom (UK), the disease has once again become endemic, according to the Health Protection Agency (HPA), the public health body of England and Wales. In an update on measles cases in its weekly bulletin last week, the agency stated that, as a result of almost a decade of low mumps-measles-rubella (MMR) vaccination coverage across the UK, 'the number of children susceptible to measles is now sufficient to support the continuous spread of measles' [1].

In an earlier update, the HPA reported that all recent indigenously-acquired cases with a genotype in England and Wales had been found to have the same D4 sequence (MVs/Enfield.GBR/14.07), a genotype first identified in April 2007 and which is now endemic in the UK [2]. In May, a 17-year-old with underlying congenital immunodeficiency died of acute measles infection, the first such fatality in the UK since 2006. The strain was also MVs/Enfield.GBR/14.07, genotype D4. The total number of confirmed measles cases in England and Wales so far this year is 461. In Scotland, there have been 68 cases of measles reported in 2008, of which 51 have been laboratory-confirmed [3]. All of the cases in Scotland were either not immunised or of unknown immunisation status. Only two of the cases were imported from abroad, both from Pakistan.

The HPA has recommended that health services exploit 'all possible opportunities' to offer MMR vaccine to children who have not received two doses. The agency also stressed the necessity for all healthcare workers in contact with vulnerable patients to have documented immunity to measles.

Europe is facing a measles epidemic, with large ongoing outbreaks for instance in Switzerland, Austria and Italy.

**References**

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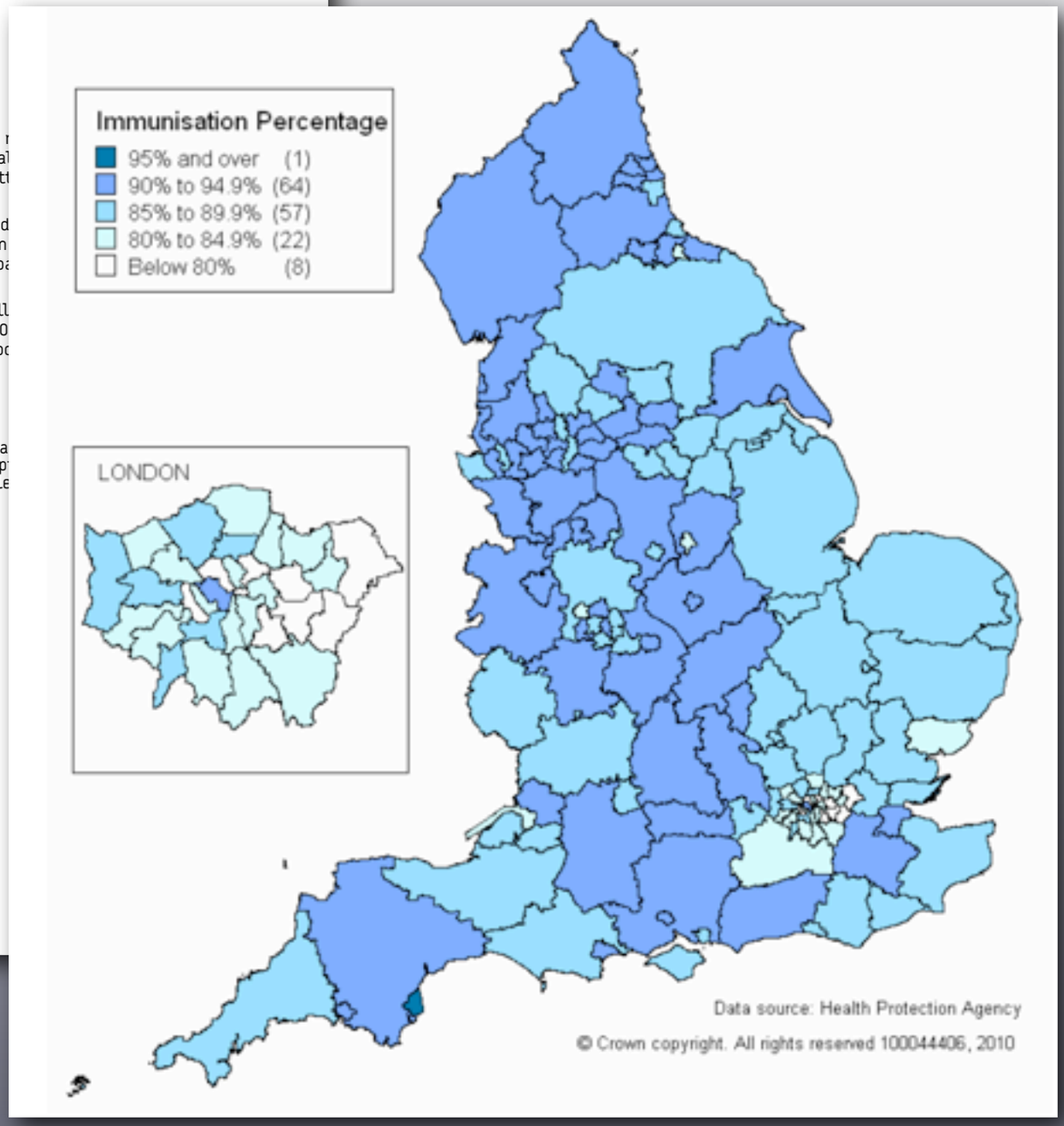
htm#meas0805
2. Health Protection Agency. Confirmed
Wales – an update. Health Protection
2;(21). Available from: http://www.hpa
htm#measls
3. Vaccine uptake, measles, mumps, rubell
Health Protection Scotland. 25 June 20
www.documents.hps.scot.nhs.uk/ewr/pd

This article was published on 3 July 2008.

Citation style for this article: Editorial tea
United Kingdom. Euro Surveill. 2008;13(27):p
eurosurveillance.org/ViewArticle.aspx?Article



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ORIGINAL ARTICLE

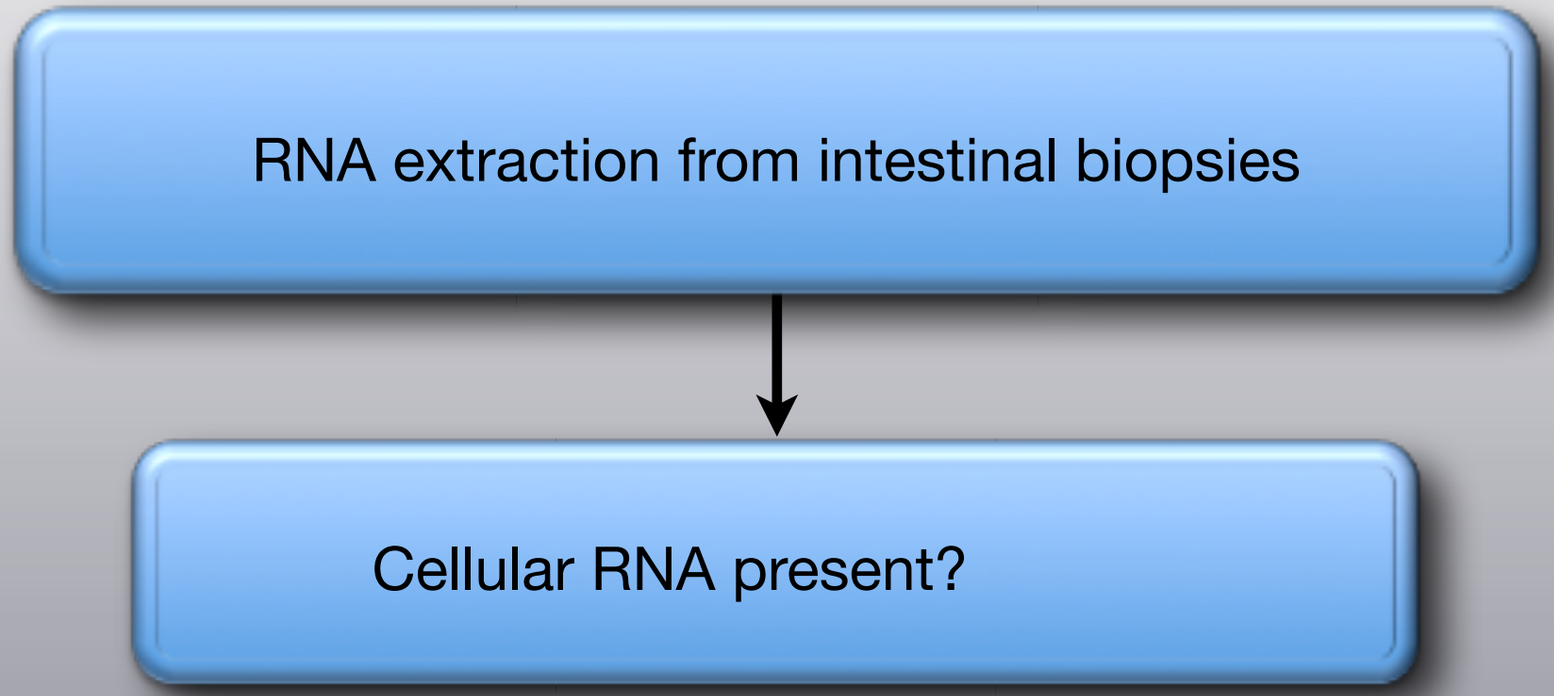
# Potential viral pathogenic mechanism for new variant inflammatory bowel disease

**V Uhlmann*, C M Martin*, O Sheils, L Pilkington, I Silva, A Killalea, S B Murch, J Walker-Smith, M Thomson, A J Wakefield, J J O'Leary**

*J Clin Pathol: Mol Pathol* 2002;**55**:84–90

**Results:** Seventy five of 91 patients with a histologically confirmed diagnosis of ileal lymphonodular hyperplasia and enterocolitis were positive for measles virus in their intestinal tissue compared with five of 70 control patients. Measles virus was identified within the follicular dendritic cells and some lymphocytes in foci of reactive follicular hyperplasia. The copy number of measles virus ranged from one to 300 000 copies/ng total RNA.
**Conclusions:** The data confirm an association between the presence of measles virus and gut pathology in children with developmental disorder.

# Uhlmann paper SOP



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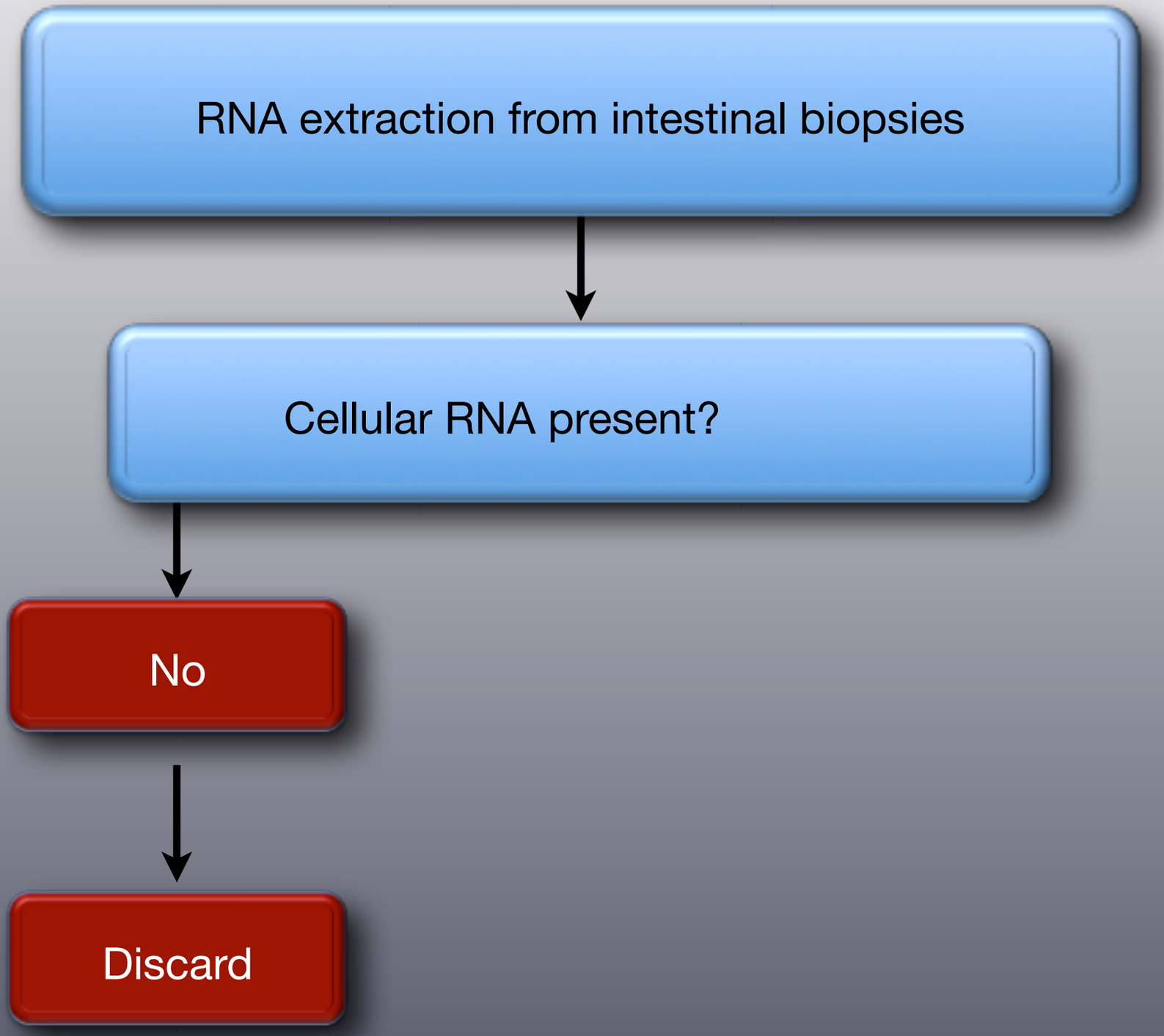
# Uhlmann paper SOP



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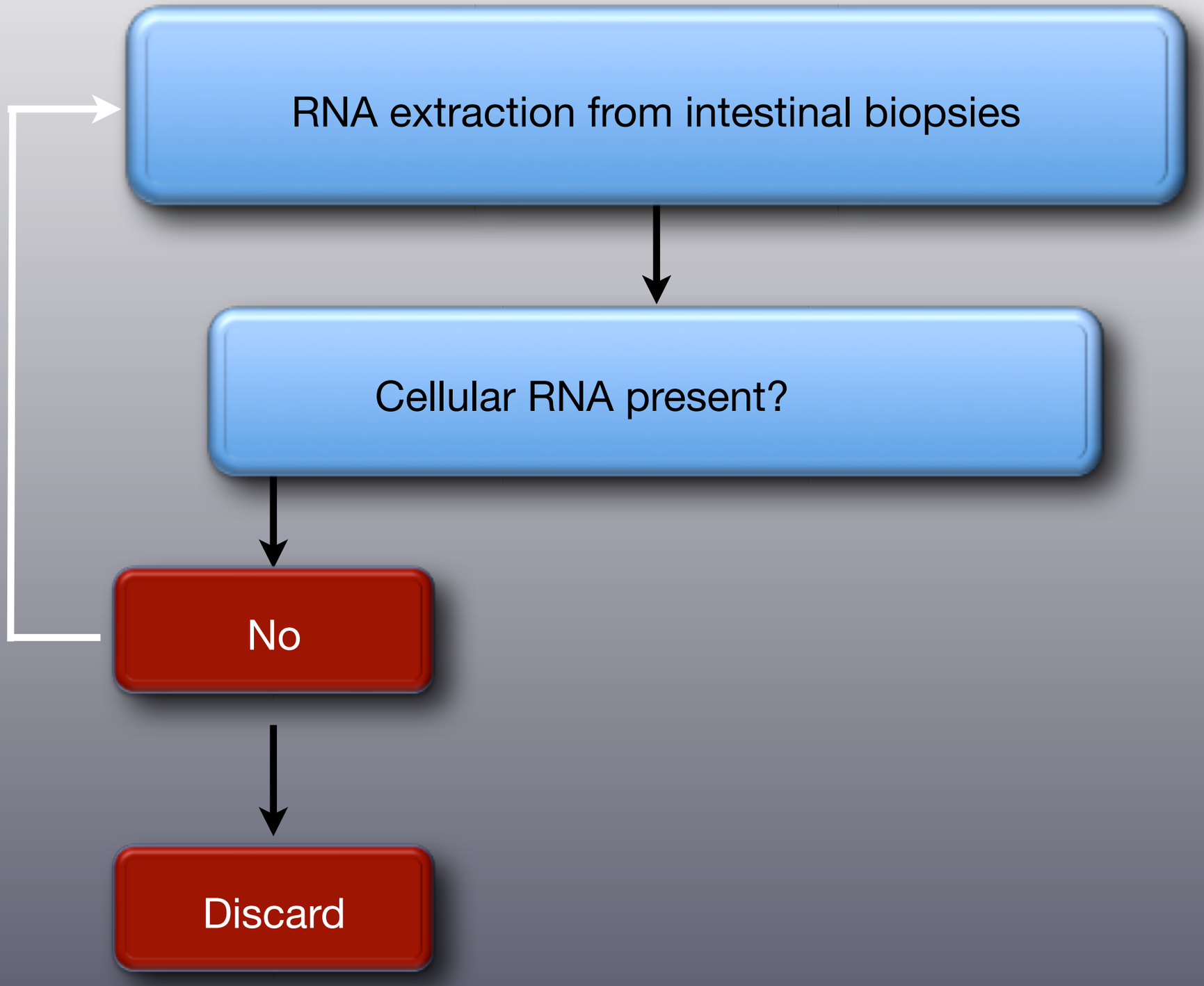
# Uhlmann paper SOP



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# Uhlmann paper SOP

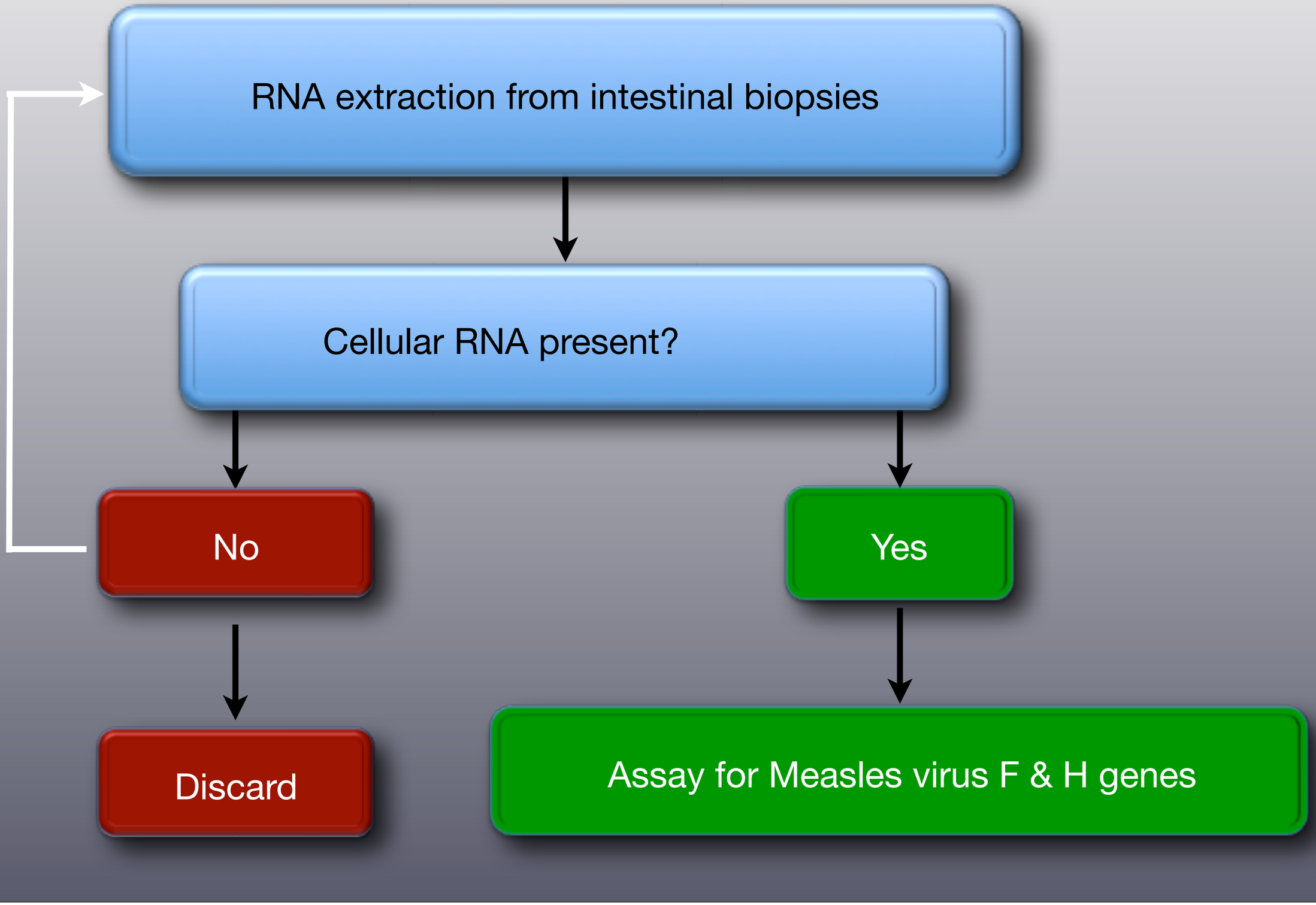

**Table 2** Summary of TaqMan RT-PCR and RT in situ PCR results

| | TaqMan RT-PCR positive | In situ PCR positive |
|---|---|---|
| Affected patients | 70 (91) | 42 (57) |
| Controls | | |
| Normal controls | 0 (19) | 1 (5) |
| Mild non-specific changes | 0 (13) | NT |
| Lymphonular hyperplasia | 0 (3) | NT |
| Appendicectomies | 4 (26) | NT |
| Ulcerative colitis | 0 (1) | NT |
| Crohn's disease | 0 (8) | NT |

Total number of patients tested in parentheses.
NT not tested; RT-PCR, reverse transcription polymerase chain reaction.

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# Is measles virus present ?

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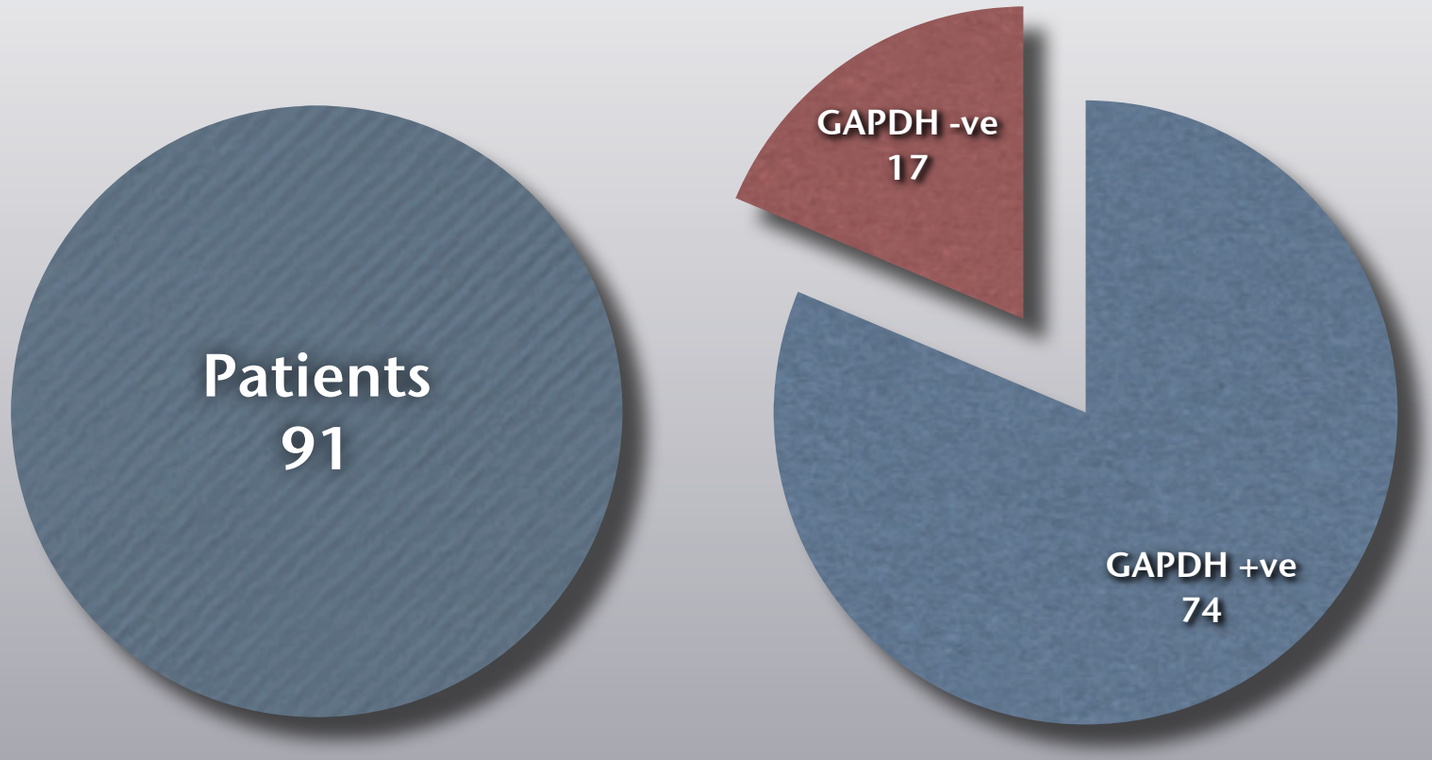
# Is measles virus present ?



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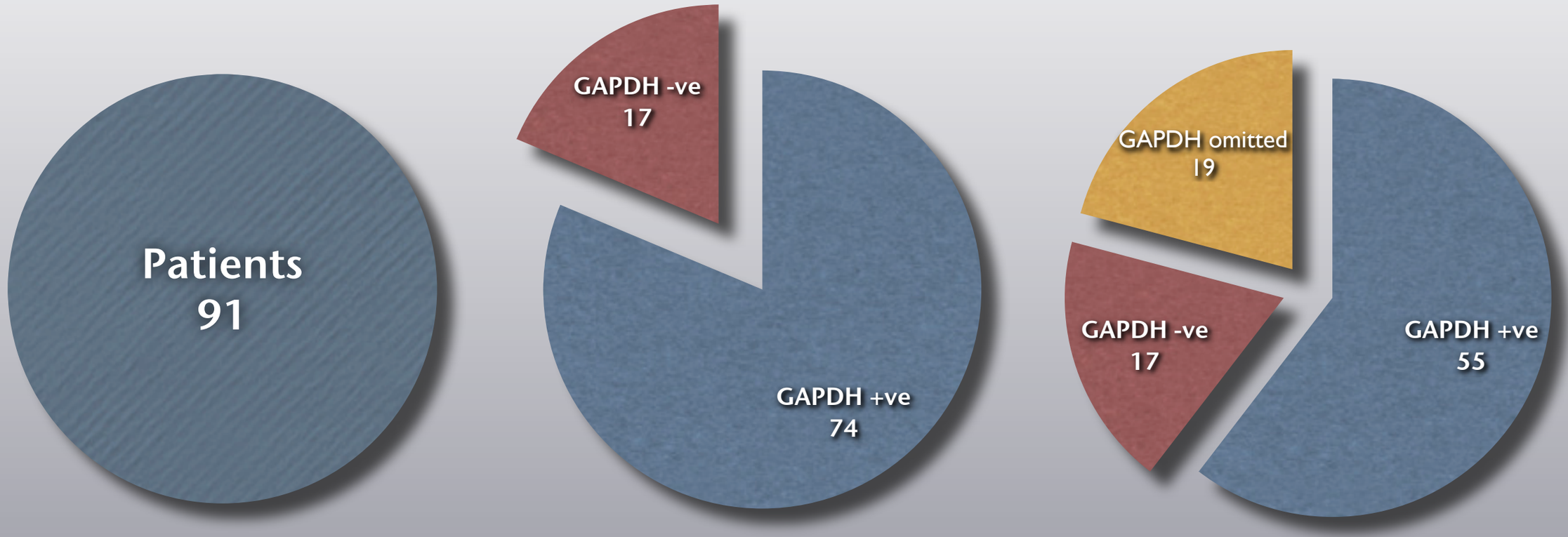
# Is measles virus present ?



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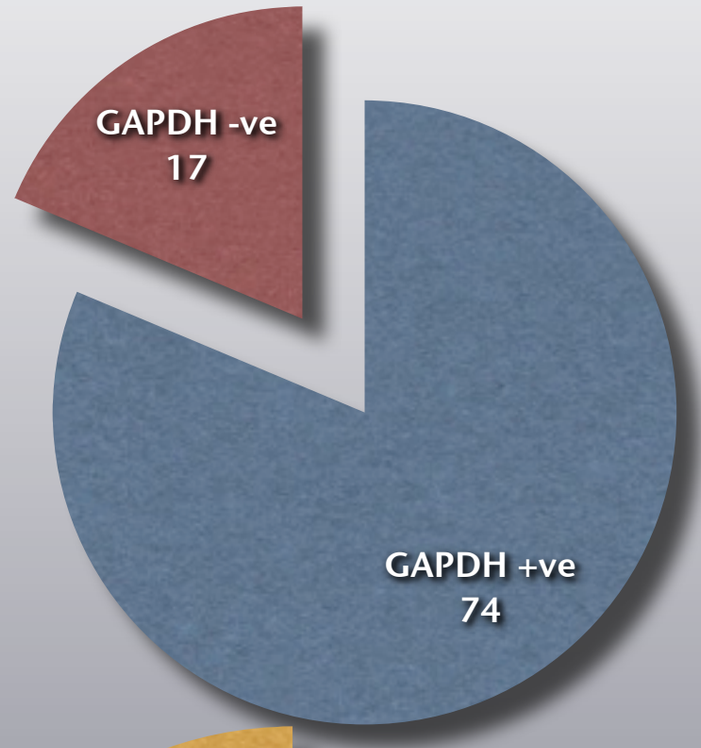
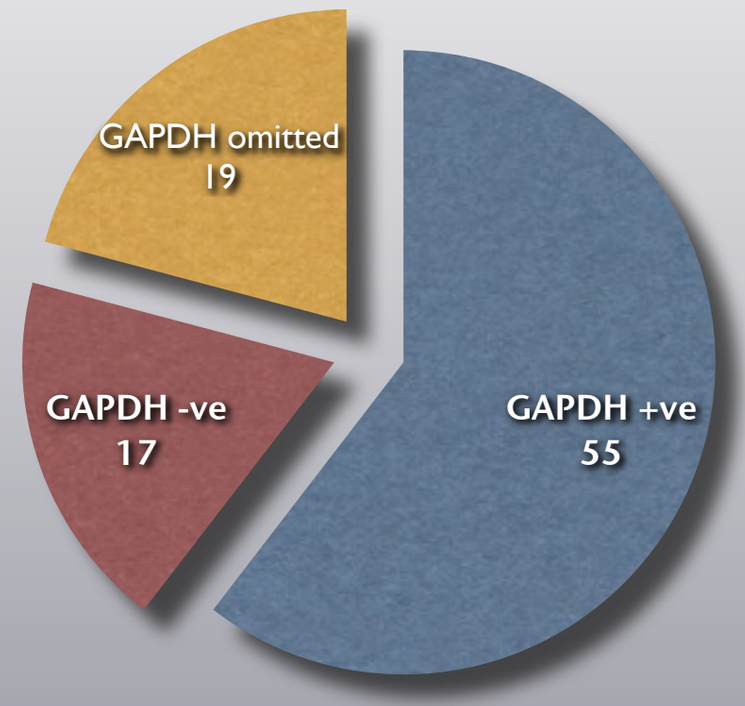
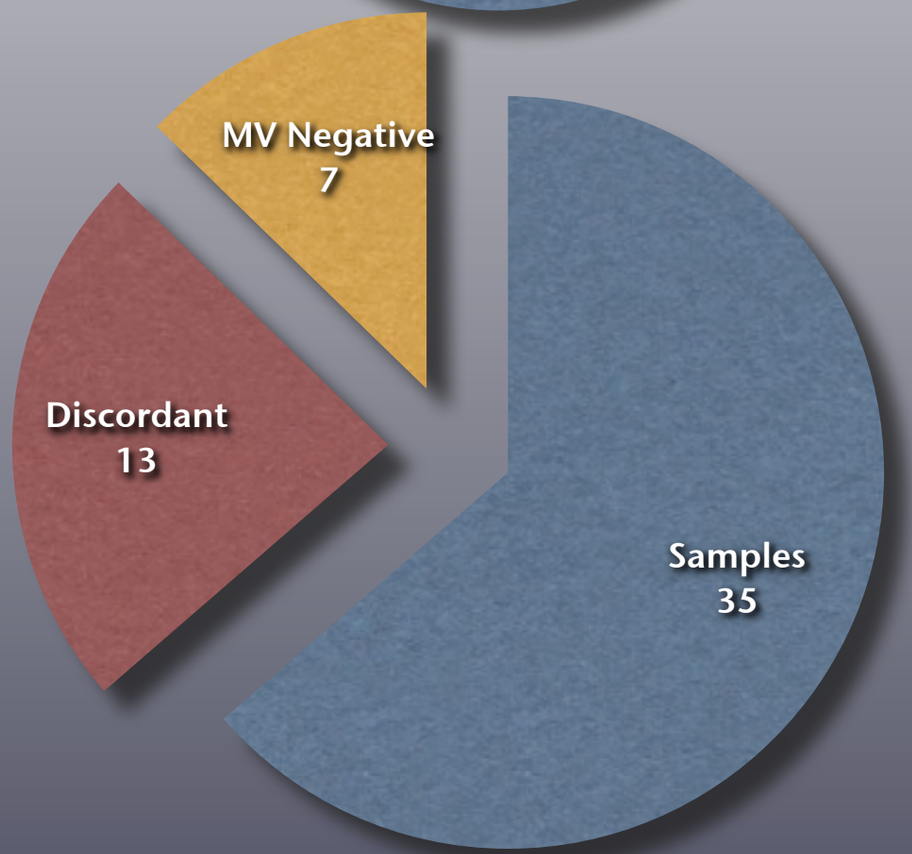
# Is measles virus present ?



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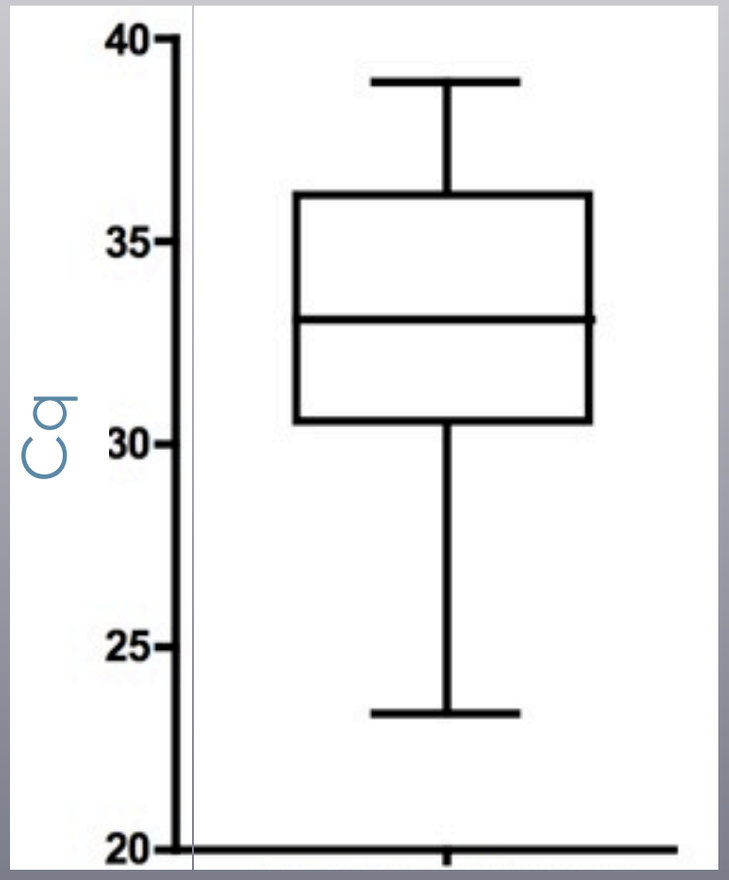
# Detection of MV target




Reference gene$^{+ve}$ samples

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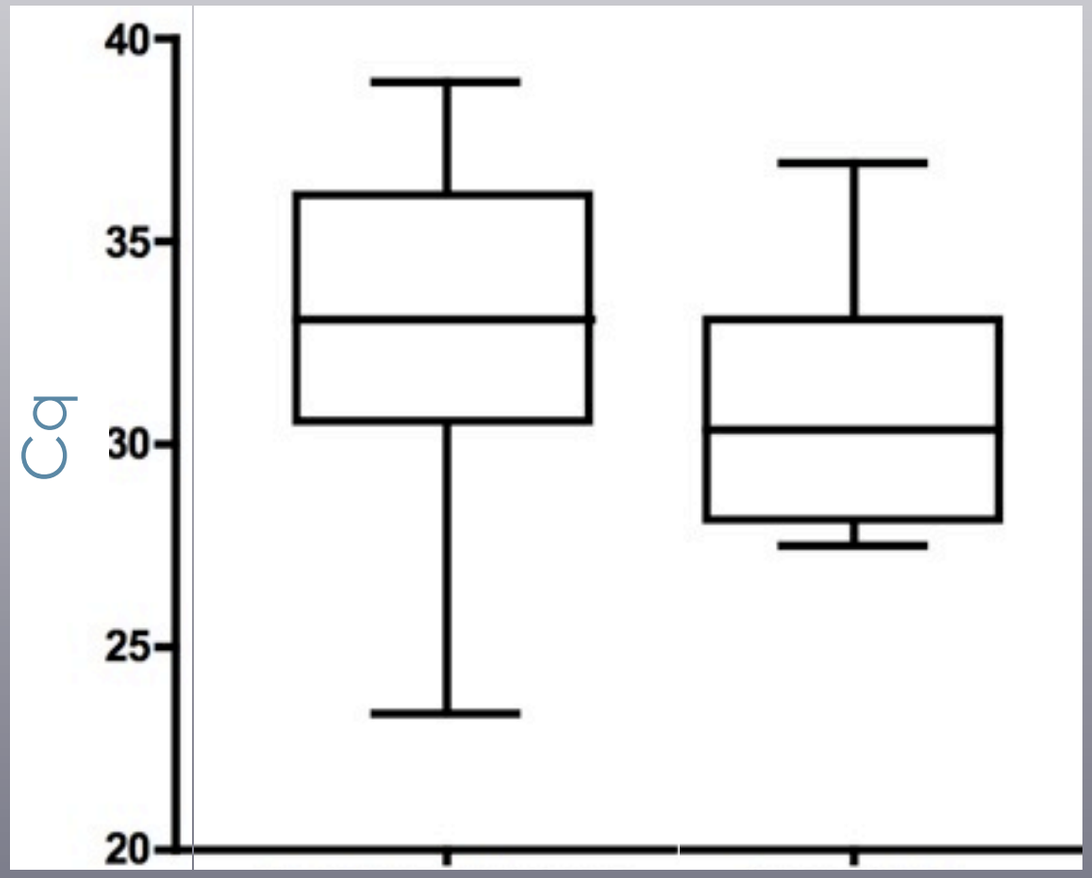
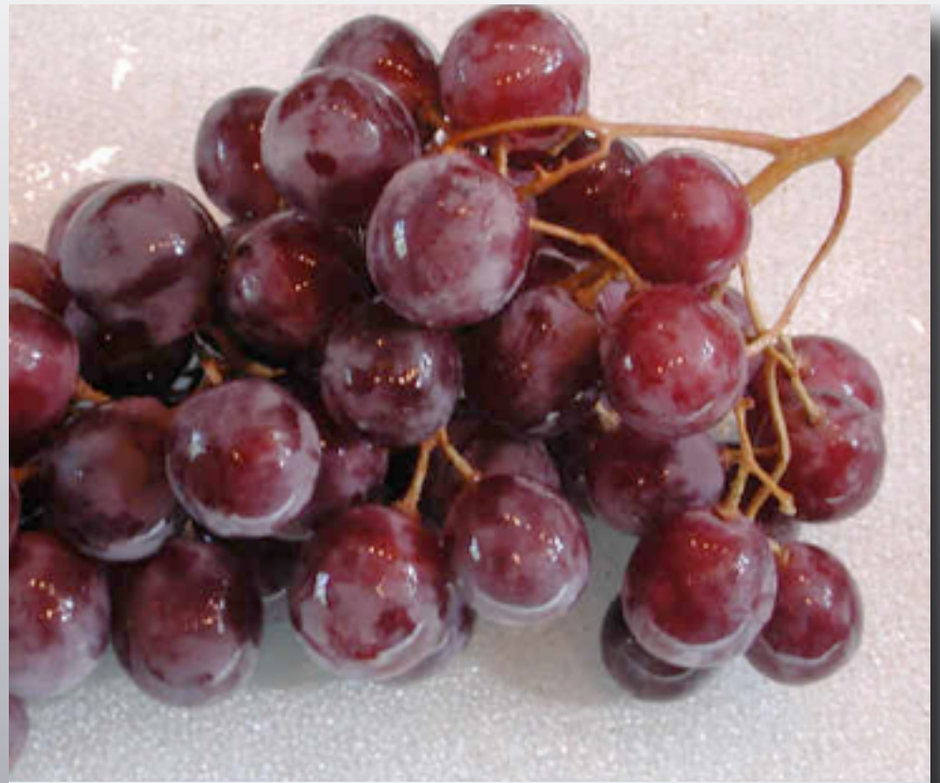
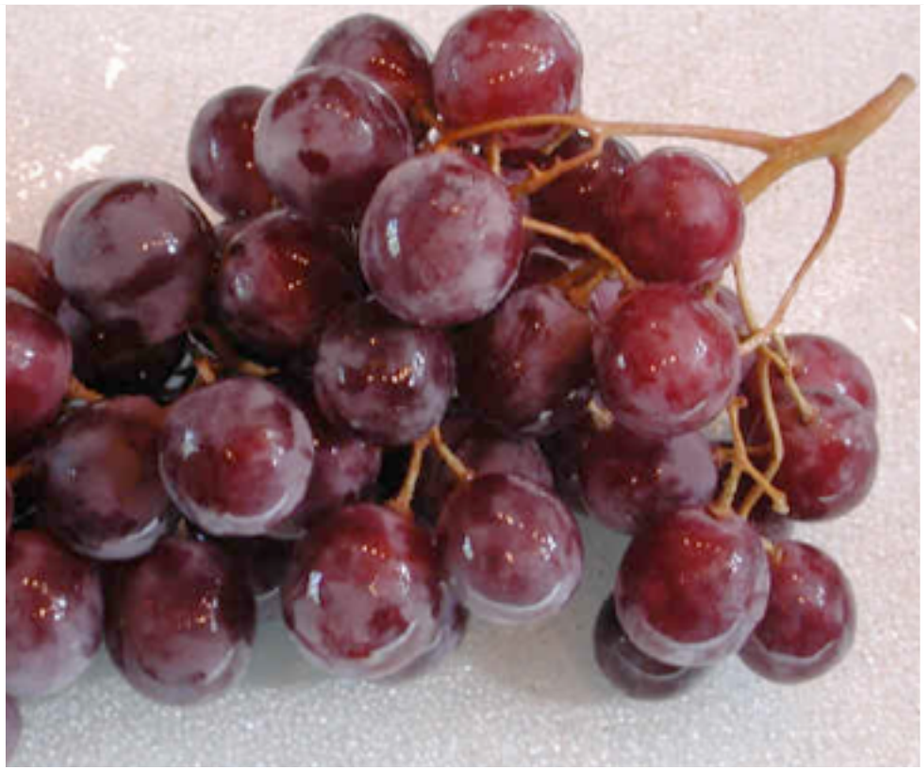
# Detection of MV target

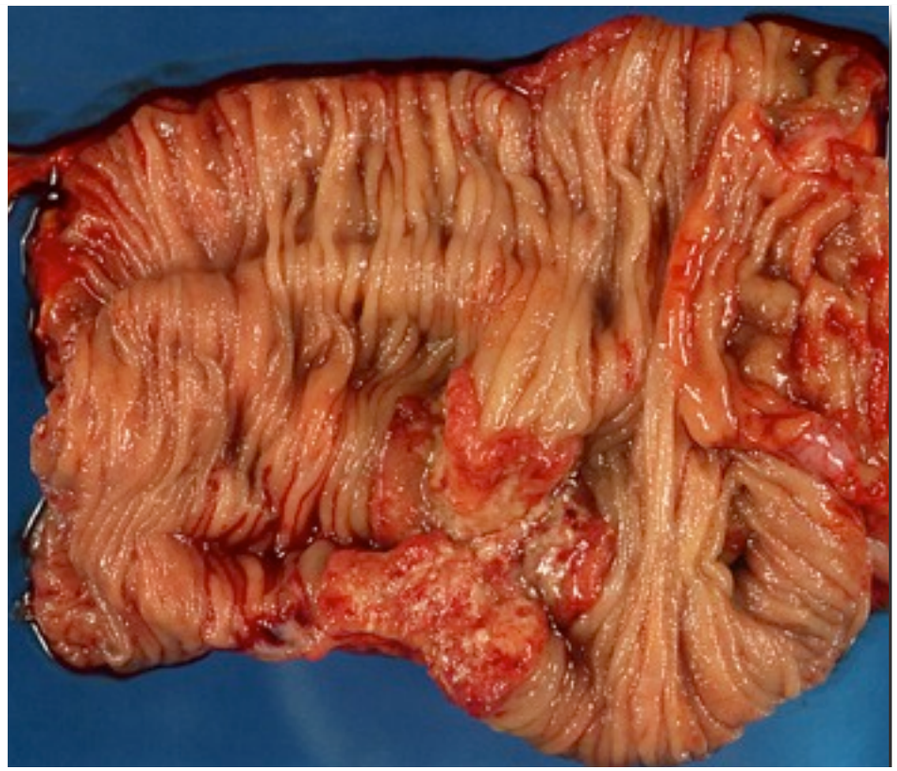



Reference gene$^{+ve}$ samples ✓

Reference gene$^{-ve}$ samples ✗







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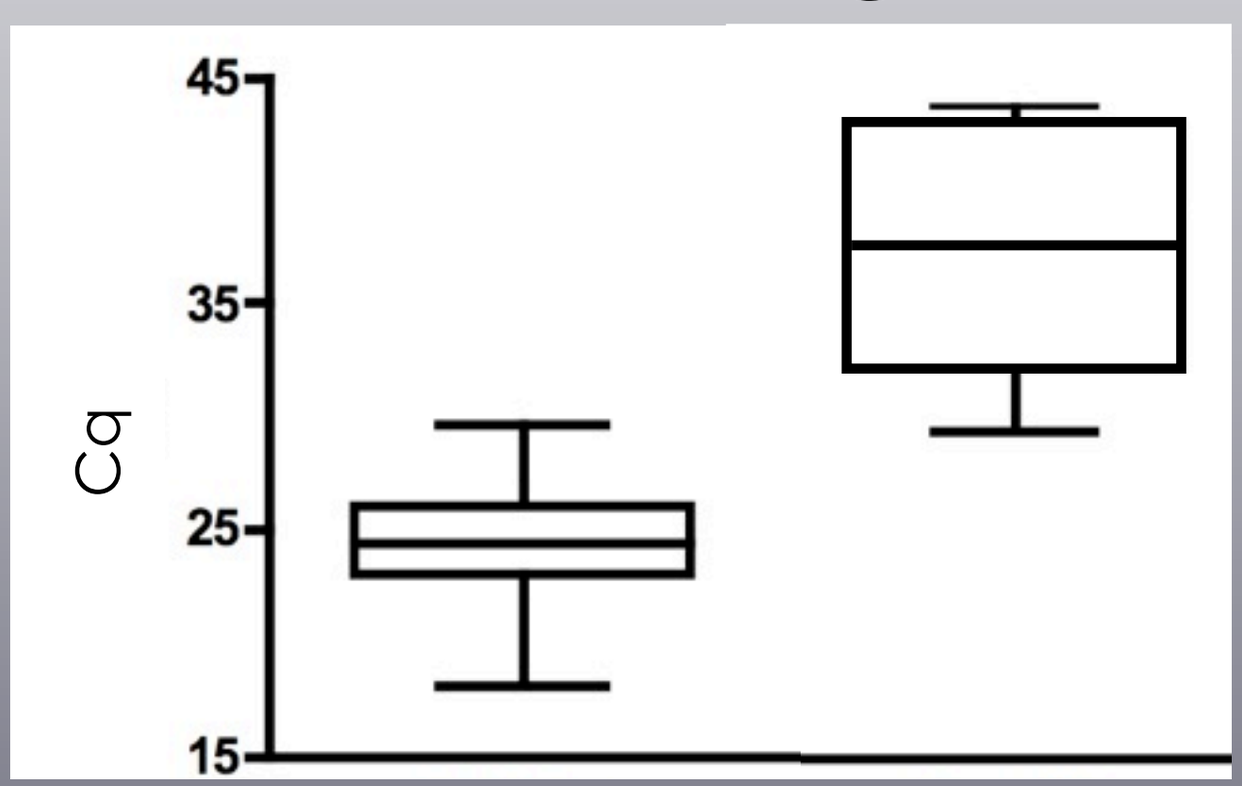
# Formalin Fixation

## Reference gene



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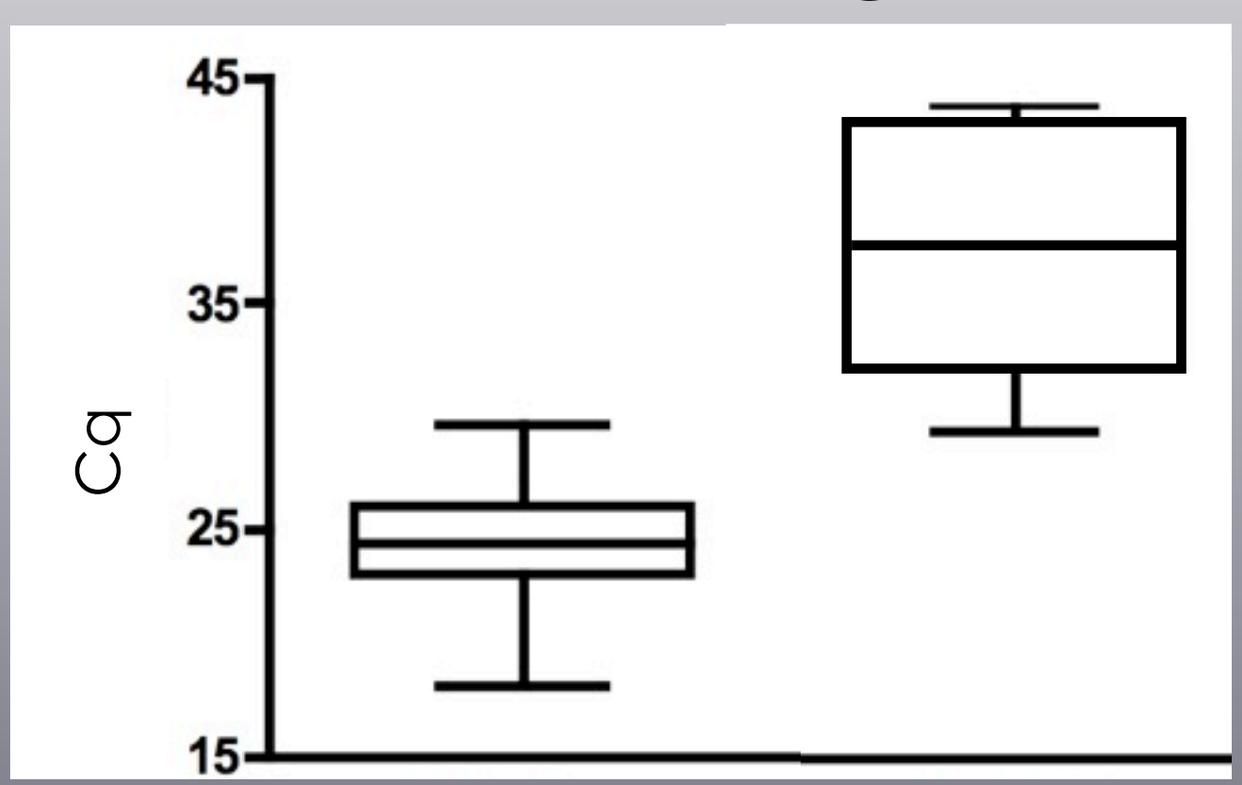
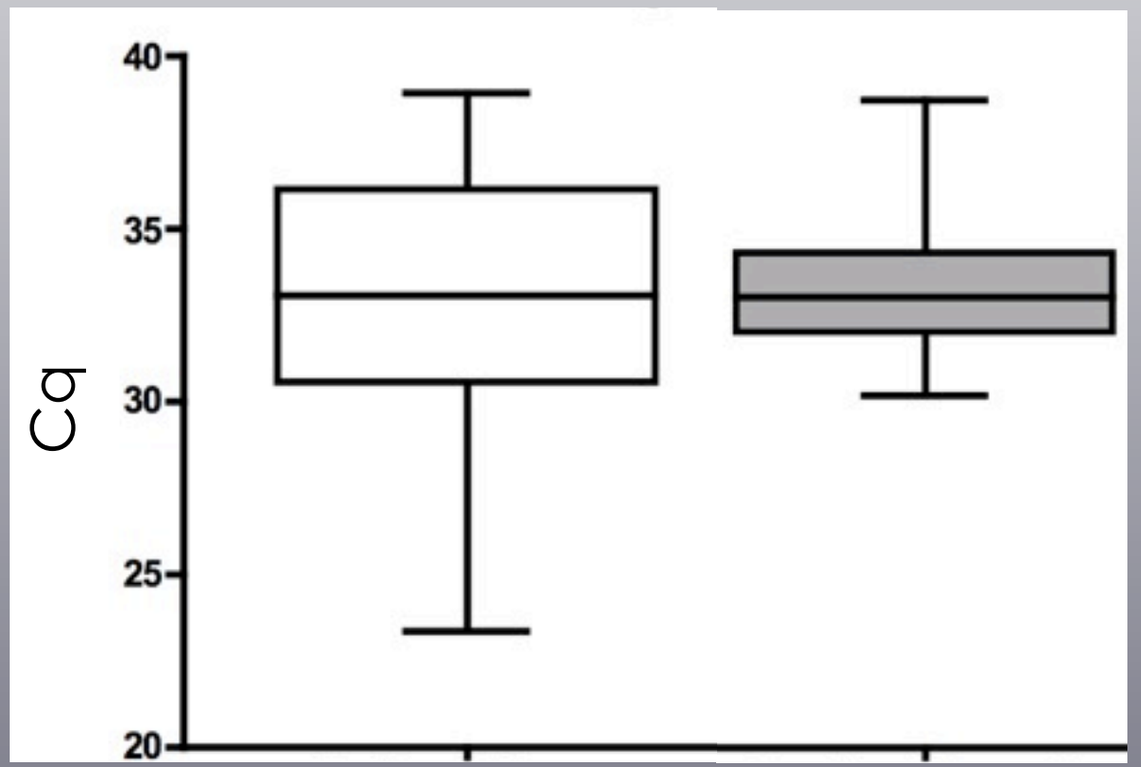
# Formalin Fixation

## Reference gene




## MV F-gene



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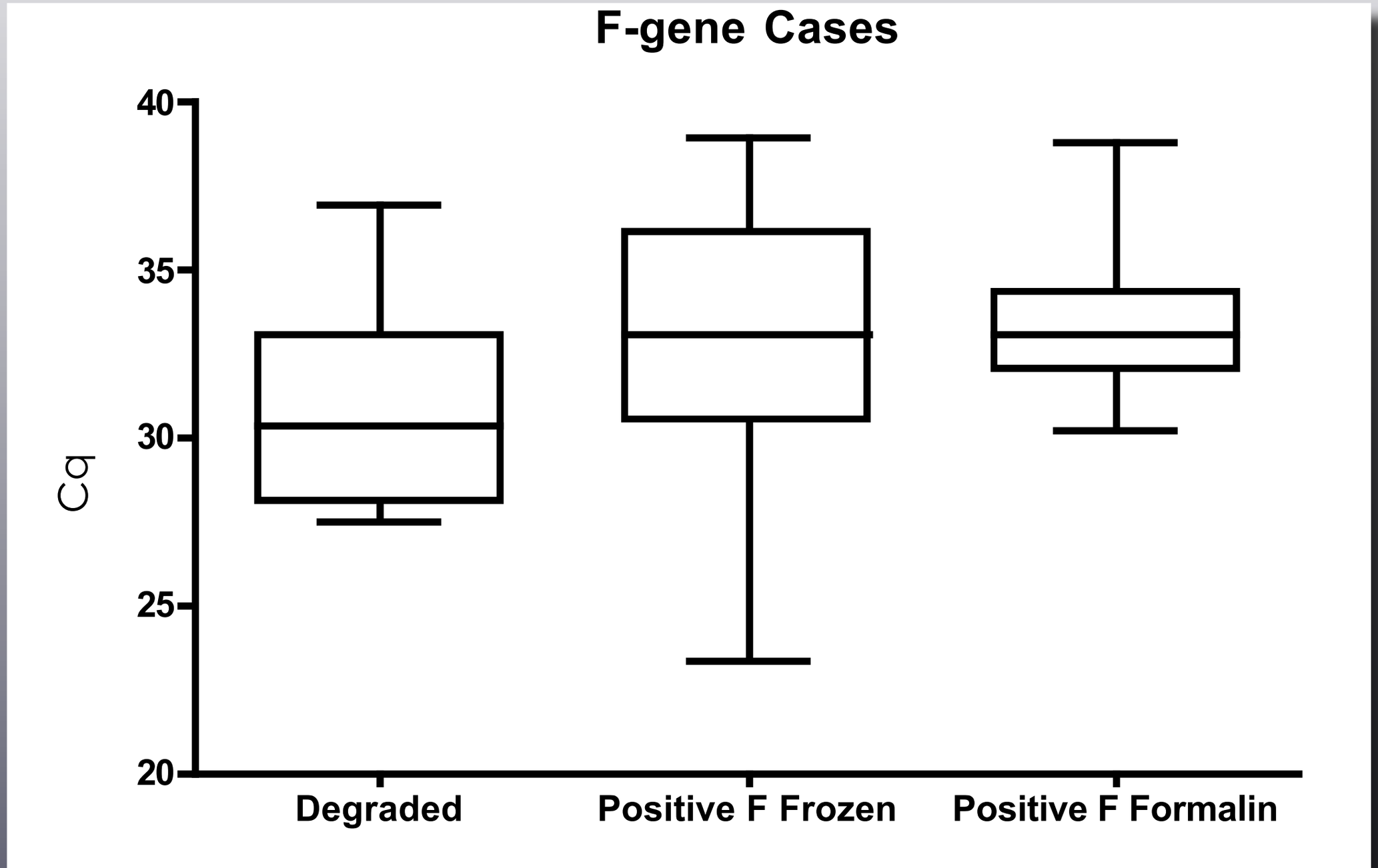
# Summary MV results



Fgene SJ 2

**Sample Type:** STND - Standard

**Sample Name:**

**Replicate:**

**Quantity:**

**Thermal Cycler Conditions**

**7700 Single Reporter Standard Plate**

**Comment:**

Show Analysis | Dye Layer: FAM

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **A** | STND 14.1 25... 5.0e+07 | STND 14.1 25... 5.0e+07 | STND 14.1 25... 5.0e+06 | STND 14.1 25... 5.0e+06 | STND 14.1 25... 5.0e+05 | STND 14.1 25... 5.0e+05 | STND 14.1 25... 5.0e+04 | STND 14.1 25... 5.0e+04 | STND 14.1 25... 5.0e+03 | STND 14.1 25... 5.0e+03 | UNKN 14.1 25... 8.0e+06 | UNKN 14.1 25... 1.0e+07 |
| **B** | UNKN 14.1 25... 1.3e+06 | UNKN 14.1 25... 1.4e+06 | UNKN 14.1 25... 1.9e+05 | UNKN 14.1 25... 1.5e+05 | UNKN 14.1 25... 3.0e+04 | UNKN 14.1 25... 3.3e+04 | UNKN 14.1 25... 1.8e+04 | UNKN 14.1 25... 1.5e+04 | UNKN 1 2.1e+02 | UNKN 1 1.6e+02 | UNKN 2 4.1e+01 | UNKN 2 7.5e+01 |
| **C** | UNKN 3 9.7e+01 | UNKN 3 1.4e+02 | UNKN 4 6.7e+00 | UNKN 4 4.5e+01 | UNKN 5 1.9e+02 | UNKN 5 3.7e+02 | UNKN 6 1.0e+01 | UNKN 6 1.3e+01 | UNKN 7 9.6e+00 | UNKN 7 1.5e+01 | UNKN 8 1.9e+01 | UNKN 8 3.3e+00 |
| **D** | UNKN 9 7.3e+01 | UNKN 9 7.3e+01 | UNKN 11 9.8e+00 | UNKN 11 1.0e+01 | UNKN 10 | UNKN 10 | UNKN 12 8.6e+00 | UNKN 12 3.0e+01 | UNKN 13 3.0e+02 | UNKN 13 2.5e+02 | UNKN 14 2.7e+02 | UNKN 14 2.1e+02 |
| **E** | UNKN 15 8.3e+01 | UNKN 15 6.7e+01 | NTC E3 | | | | | | | | | |
| **F** | | | | | | | | | | | | |
| **G** | | | | | | | | | | | | |
| **H** | | | | | | | | | | | | |

Fgene SJ 2

**Sample Type:** NTC - No Template Cont...

**Sample Name:**

**Replicate:**

**Quantity:**

**Thermal Cycler Conditions**

**7700 Single Reporter Standard Plate**

**Comment:**

Show Analysis | Dye Layer: FAM

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| **C** | UNKN 3 1.7e+02 | UNKN 3 2.5e+02 | UNKN 4 9.4e+00 | UNKN 4 6.8e+01 | UNKN 5 2.1e+02 | UNKN 5 1.1e+03 | UNKN 6 1.7e+01 | UNKN 6 2.3e+01 | UNKN 7 1.0e+01 | UNKN 7 1.7e+01 | UNKN 8 2.7e+01 | UNKN 8 2.9e+00 |
| **D** | UNKN 9 7.4e+01 | UNKN 9 9.7e+01 | UNKN 11 1.4e+01 | UNKN 11 9.4e+00 | UNKN 10 | UNKN 10 | UNKN 12 1.1e+01 | UNKN 12 3.6e+01 | UNKN 13 4.3e+02 | UNKN 13 2.7e+02 | UNKN 14 4.1e+02 | UNKN 14 2.9e+02 |
| **E** | UNKN 15 1.5e+02 | UNKN 15 7.5e+01 | NTC E3 | NTC E4 | | | | | | | | |
| **F** | | | | | | | | | | | | |
| **G** | | | | | | | | | | | | |
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Fgene SJ 2

Sample Type: NTC - No Template Cont...
Sample Name:
Replicate:
Quantity:

Thermal Cycler Conditions

7700 Single Reporter
Standard Plate

Comment:

Show Analysis | Dye Layer: FAM

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| B | UNKN 14.1 25... 1.1e+06 | UNKN 14.1 25... 1.3e+06 | UNKN 14.1 25... 1.7e+05 | UNKN 14.1 25... 1.7e+05 | UNKN 14.1 25... 2.7e+04 | UNKN 14.1 25... 2.9e+04 | UNKN 14.1 25... 1.7e+04 | UNKN 14.1 25... 1.3e+04 | UNKN 1 2.7e+02 | UNKN 1 3.4e+02 | UNKN 2 7.7e+01 | UNKN 2 1.2e+02 |
| C | UNKN 3 1.7e+02 | UNKN 3 2.5e+02 | UNKN 4 9.4e+00 | UNKN 4 6.8e+01 | UNKN 5 2.1e+02 | UNKN 5 1.1e+03 | UNKN 6 1.7e+01 | UNKN 6 2.3e+01 | UNKN 7 1.0e+01 | UNKN 7 1.7e+01 | UNKN 8 2.7e+01 | UNKN 8 2.9e+00 |
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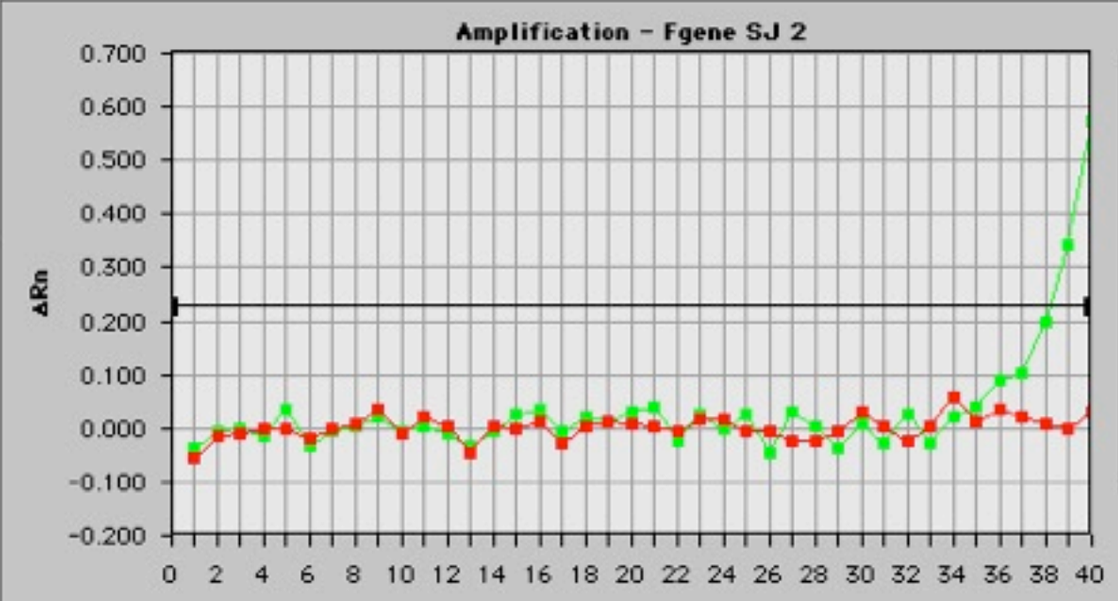
| E | UNKN 15 1.5e+02 | UNKN 15 7.5e+01 | NTC E3 | NTC E4 | | | | | | | | |

Amplification Plot

Amplification - Fgene SJ 2




Samples
FAM - E3
FAM - E4

Viewer: ΔRn (B...
Reporter: FAM

Threshold Cycle Calculation

Threshold
Use Threshold: .228 Suggest
Mult. * Stddev: 10.0 * .023
Omit Threshold: 2.0

Baseline
Start: 3 Stop: 15

| | Ct | Std Dev |
|---|---|---|
| FAM - E3 | 40.000 | 0.019 |
| FAM - E4 | 38.200 | 0.020 |

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Fgene SJ 2

Sample Type: NTC – No Template Cont...
Sample Name:
Replicate:
Quantity:

Thermal Cycler Conditions

7700 Single Reporter
Standard Plate

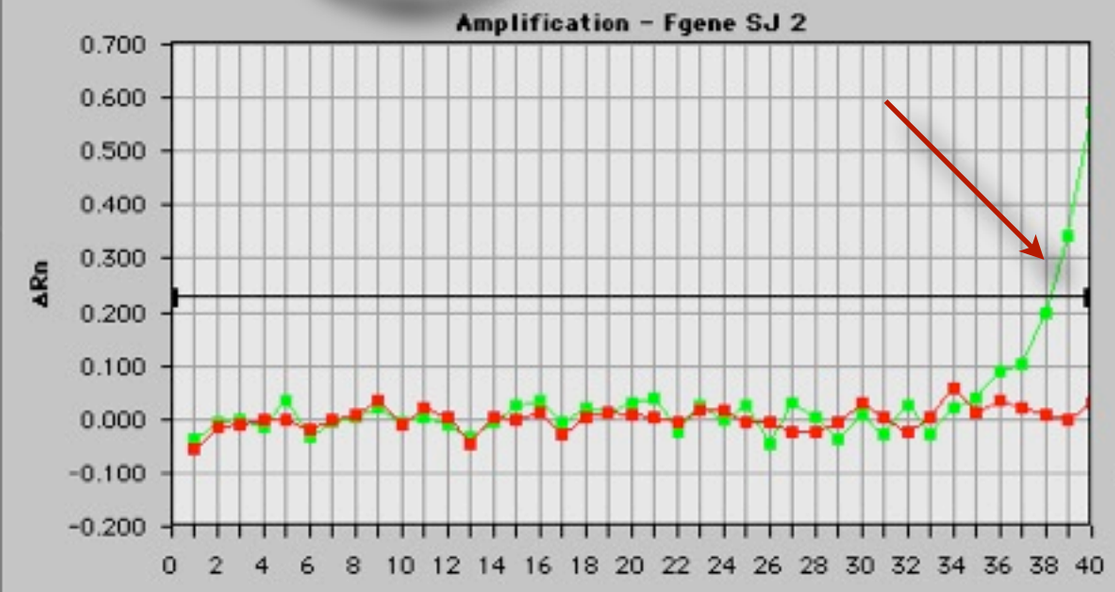
Comment:

Show Analysis | Dye Layer: FAM

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | STND 14.1 25... 5.0e+07 | STND 14.1 25... 5.0e+07 | STND 14.1 25... 5.0e+06 | STND 14.1 25... 5.0e+06 | STND 14.1 25... 5.0e+05 | STND 14.1 25... 5.0e+05 | STND 14.1 25... 5.0e+04 | STND 14.1 25... 5.0e+04 | STND 14.1 25... 5.0e+03 | STND 14.1 25... 5.0e+03 | UNKN 14.1 25... 8.2e+06 | UNKN 14.1 25... 9.4e+06 |
| B | UNKN 14.1 25... 1.1e+06 | UNKN 14.1 25... 1.3e+06 | UNKN 14.1 25... 1.7e+05 | UNKN 14.1 25... 1.7e+05 | UNKN 14.1 25... 2.7e+04 | UNKN 14.1 25... 2.9e+04 | UNKN 14.1 25... 1.7e+04 | UNKN 14.1 25... 1.3e+04 | UNKN 1 2.7e+02 | UNKN 1 3.4e+02 | UNKN 2 7.7e+01 | UNKN 2 1.2e+02 |
| C | UNKN 3 1.7e+02 | UNKN 3 2.5e+02 | UNKN 4 9.4e+00 | UNKN 4 6.8e+01 | UNKN 5 2.1e+02 | UNKN 5 1.1e+03 | UNKN 6 1.7e+01 | UNKN 6 2.3e+01 | UNKN 7 1.0e+01 | UNKN 7 1.7e+01 | UNKN 8 2.7e+01 | UNKN 8 2.9e+00 |
| D | UNKN 9 7.4e+01 | UNKN 9 9.7e+01 | UNKN 11 [illegible]e+01 | UNKN 11 9.4e+00 | UNKN 10 | UNKN 10 | UNKN 12 1.1e+01 | UNKN 12 3.6e+01 | UNKN 13 4.3e+02 | UNKN 13 2.7e+02 | UNKN 14 4.1e+02 | UNKN 14 2.9e+02 |
| E | UNKN 15 1.5e+02 | UNKN 15 7.5e+01 | NTC E3 | NTC E4 | | | | | | | | |

Amplification Plot

Amplification – Fgene SJ 2




Samples
FAM – E3
FAM – E4

Viewer: ΔRn (B...
Reporter: FAM

Threshold Cycle Calculation

Threshold
Use Threshold: .228 Suggest
Mult. * Stddev: 10.0 * .023
Omit Threshold: 2.0

Baseline
Start: 3 Stop: 15

| | Ct | Std Dev |
|---|---|---|
| FAM – E3 | 40.000 | 0.019 |
| FAM – E4 | 38.200 | 0.020 |

F Gene run 20-09-00.2

**Sample Type:** STND - Standard
**Sample Name:** 14.1 260
**Replicate:**
**Quantity:** 5.0e+04

**Thermal Cycler Conditions**

**7700 Single Reporter Standard Plate**

**Comment:**

Show Analysis | Dye Layer: FAM

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **A** | STND 14.1 260 5.0e+08 | STND 14.1 260 5.0e+08 | STND 14.1 260 5.0e+07 | STND 14.1 260 5.0e+07 | STND 14.1 260 5.0e+06 | STND 14.1 260 5.0e+06 | STND 14.1 260 5.0e+05 | STND 14.1 260 5.0e+05 | STND 14.1 260 5.0e+04 | STND 14.1 260 5.0e+04 | UNKN A11 5.2e+08 | UNKN A12 4.2e+08 |
| **B** | UNKN B1 1.3e+08 | UNKN B2 1.5e+08 | UNKN B3 9.6e+06 | UNKN B4 9.7e+06 | UNKN B5 9.8e+03 | UNKN B6 8.1e+03 | UNKN B7 2.6e+02 | UNKN B8 3.3e+02 | NAC B9 | NAC B10 | NTC B11 | |
| **C** | UNKN 38 | UNKN 38 7.3e+00 | UNKN 39 | UNKN 39 2.8e+01 | UNKN 41 1.2e+01 | UNKN 41 1.8e+00 | UNKN 45 2.3e+01 | UNKN 45 1.8e+01 | UNKN 46 | UNKN 46 4.2e+01 | UNKN 47 | UNKN 47 |
| **D** | UNKN 48 2.7e+01 | UNKN 48 | UNKN 59 2.8e+02 | UNKN 59 3.4e+02 | UNKN 60 6.7e+00 | UNKN 60 | UNKN 65 1.8e+01 | UNKN 65 3.2e+01 | UNKN 108 | UNKN 108 | UNKN 130 1.2e+02 | UNKN 130 6.8e+00 |
| **E** | UNKN abram a | UNKN abram a 3.7e+01 | UNKN 14 | UNKN 14 | UNKN 27 | UNKN 27 1.5e+00 | UNKN 30 | UNKN 30 | UNKN 42 | UNKN 42 | UNKN 57 2.3e+03 | UNKN 57 2.8e+03 |
| **F** | UNKN 58 2.2e+02 | UNKN 58 2.1e+02 | UNKN 85 1.4e+03 | UNKN 85 3.0e+02 | UNKN 95 | UNKN 95 | UNKN 104 1.6e+02 | UNKN 104 4.2e+02 | UNKN 107 | UNKN 107 1.7e+01 | UNKN 110 | UNKN 110 |
| **G** | UNKN 112 | UNKN 112 | | | | | | | | | | |
| **H** | | | | | | | | | | | | |

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## F Gene run 20-09-00.2

**Sample Type:** NTC - No Template Cont...
**Sample Name:**
**Replicate:**
**Quantity:**

**Thermal Cycler Conditions**

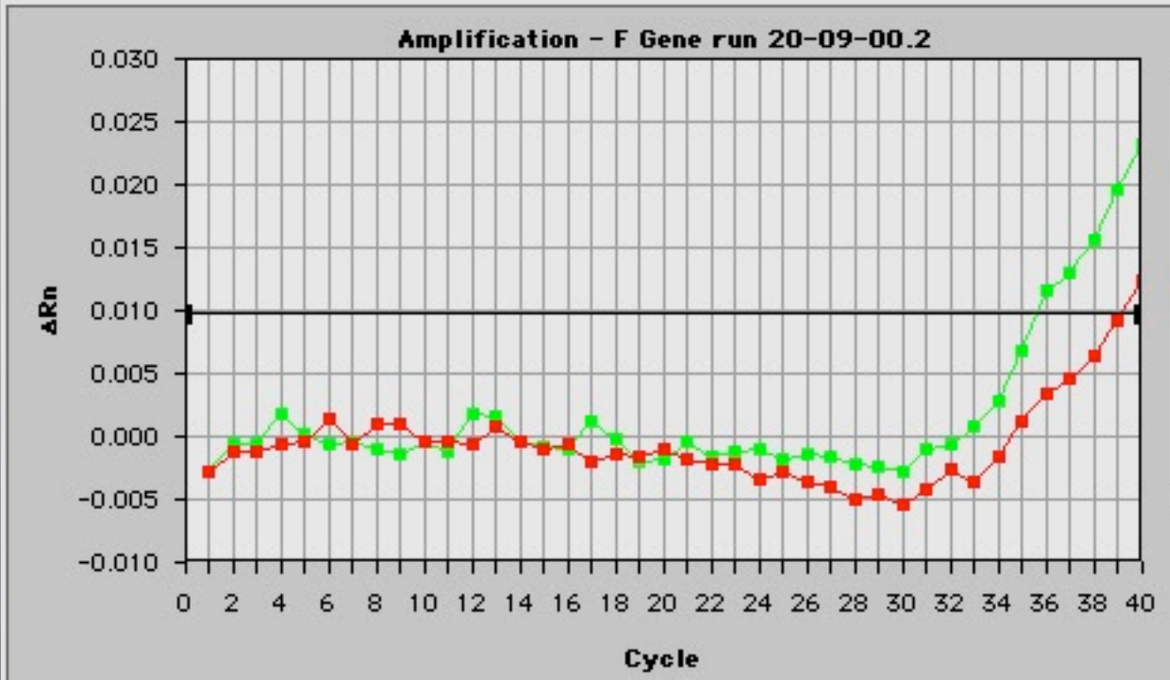
**7700 Single Reporter Standard Plate**

**Comment:**

Show Analysis | Dye Layer: FAM

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | STND 14.1 260 5.0e+08 | STND 14.1 260 5.0e+08 | STND 14.1 260 5.0e+07 | STND 14.1 260 5.0e+07 | STND 14.1 260 5.0e+06 | STND 14.1 260 5.0e+06 | STND 14.1 260 5.0e+05 | STND 14.1 260 5.0e+05 | STND 14.1 260 5.0e+04 | STND 14.1 260 5.0e+04 | UNKN A11 | UNKN A12 3.1e+08 |
| B | UNKN B1 1.3e+08 | UNKN B2 1.4e+08 | UNKN B3 1.0e+07 | UNKN B4 1.0e+07 | UNKN B5 9.7e+03 | UNKN B6 8.2e+03 | UNKN B7 2.4e+02 | UNKN B8 2.6e+02 | NAC B9 | NAC B10 | NTC B11 | NTC B12 |
| C | UNKN 38 | UNKN 38 9.5e+00 | UNKN 39 | UNKN 39 3.8e+01 | UNKN 41 4.4e+00 | UNKN 41 1.8e+00 | UNKN 45 2.6e+01 | UNKN 45 2.0e+01 | UNKN 46 | UNKN 46 3.8e+01 | UNKN 47 | UNKN 47 |

## Amplification Plot




**Samples**

- FAM - B11
- FAM - B12

Viewer: ΔRn (B...
Reporter: FAM

**Threshold Cycle Calculation**

**Threshold**

Use Threshold: .01 Suggest
Mult. * Stddev: 10.0 * .001
Omit Threshold: 2.0

**Baseline**

Start: 3 Stop: 15

Update Calculations

| | Ct | Std Dev |
|---|---|---|
| FAM - B11 | 39.236 | 0.001 |
| FAM - B12 | 35.642 | 0.001 |
| | | |
| | | |
| | | |

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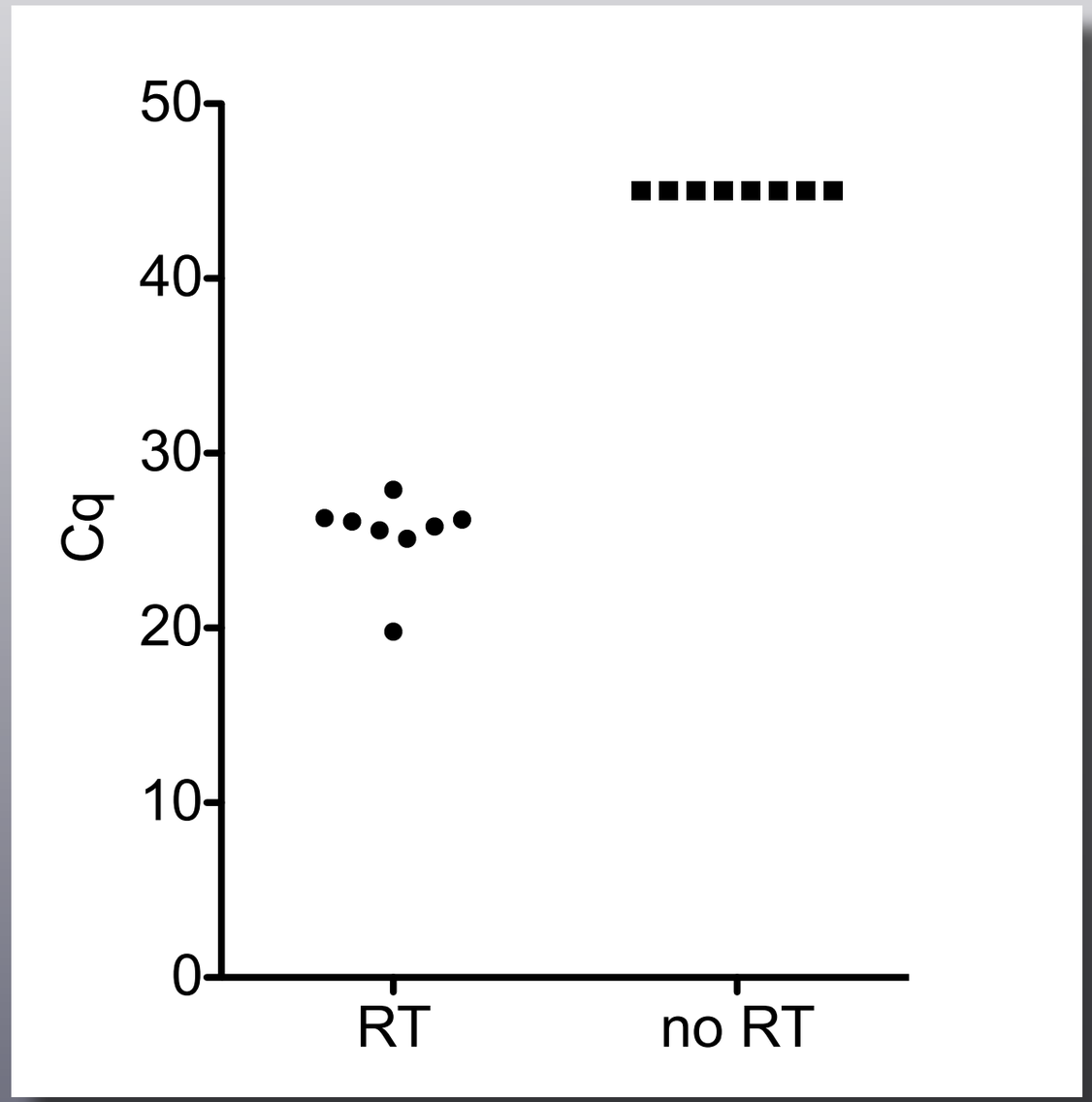
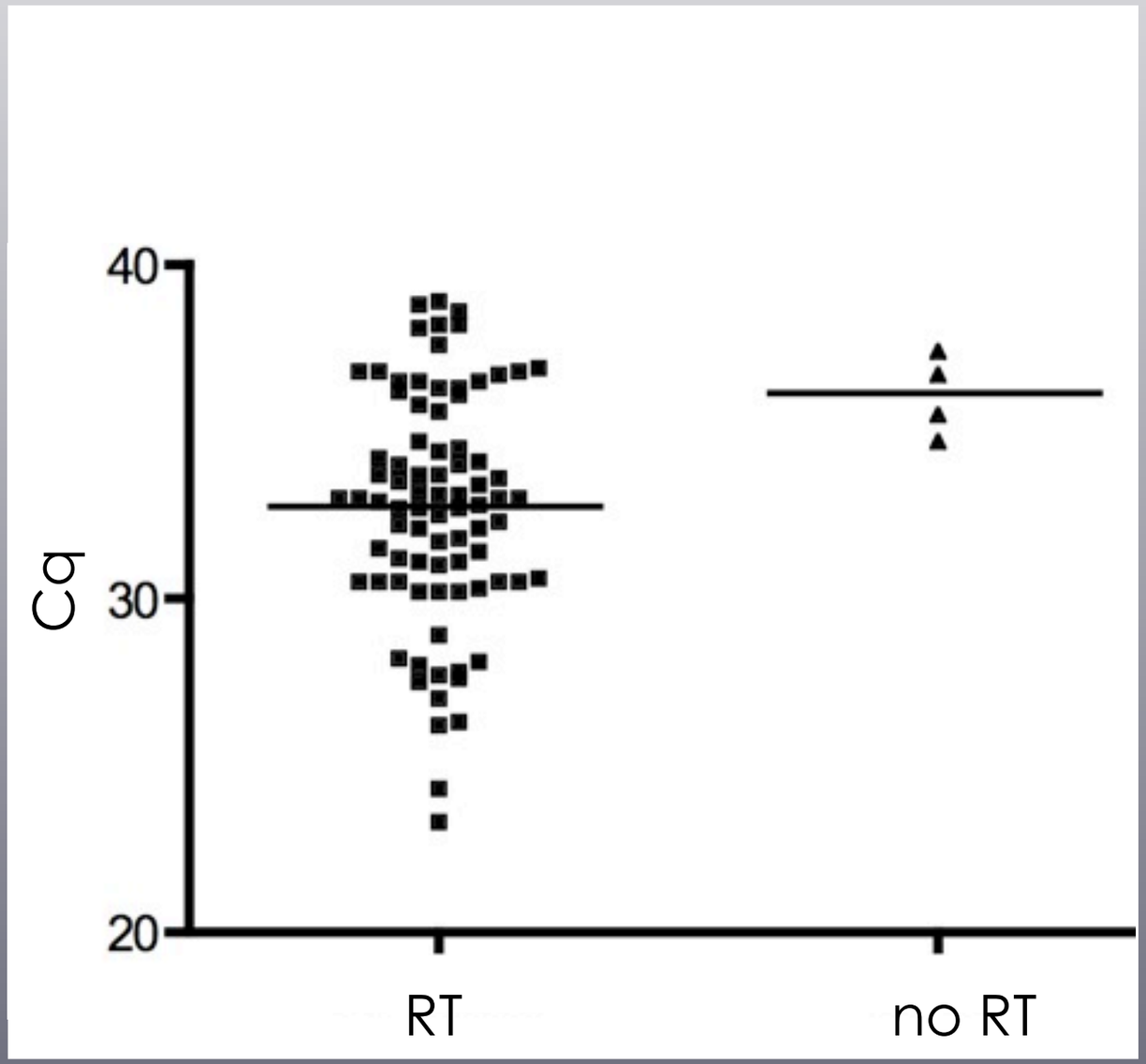
# Reference gene




# MV F-gene



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# Summary

- 30% of negative controls are positive
- Inappropriate analysis
  - negatives are reported as positives & vice versa
- Data not reproducible by independent laboratories
- Detection of DNA contamination rules out MV

# Detection of an Infectious Retrovirus, XMRV, in Blood Cells of Patients with Chronic Fatigue Syndrome

Vincent C. Lombardi,[1]* Francis W. Ruscetti,[2]* Jaydip Das Gupta,[3] Max A. Pfost,[1] Kathryn S. Hagen,[1] Daniel L. Peterson,[1] Sandra K. Ruscetti,[4] Rachel K. Bagni,[5] Cari Petrow-Sadowski,[6] Bert Gold,[2] Michael Dean,[2] Robert H. Silverman,[3] Judy A. Mikovits[1]†

Chronic fatigue syndrome (CFS) is a debilitating disease of unknown etiology that is estimated to affect 17 million people worldwide. Studying peripheral blood mononuclear cells (PBMCs) from CFS patients, we identified DNA from a human gammaretrovirus, xenotropic murine leukemia virus–related virus (XMRV), in 68 of 101 patients (67%) as compared to 8 of 218 (3.7%) healthy controls. Cell culture experiments revealed that patient-derived XMRV is infectious and that both cell-associated and cell-free transmission of the virus are possible. Secondary viral infections were established in uninfected primary lymphocytes and indicator cell lines after their exposure to activated PBMCs, B cells, T cells, or plasma derived from CFS patients. These findings raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS.

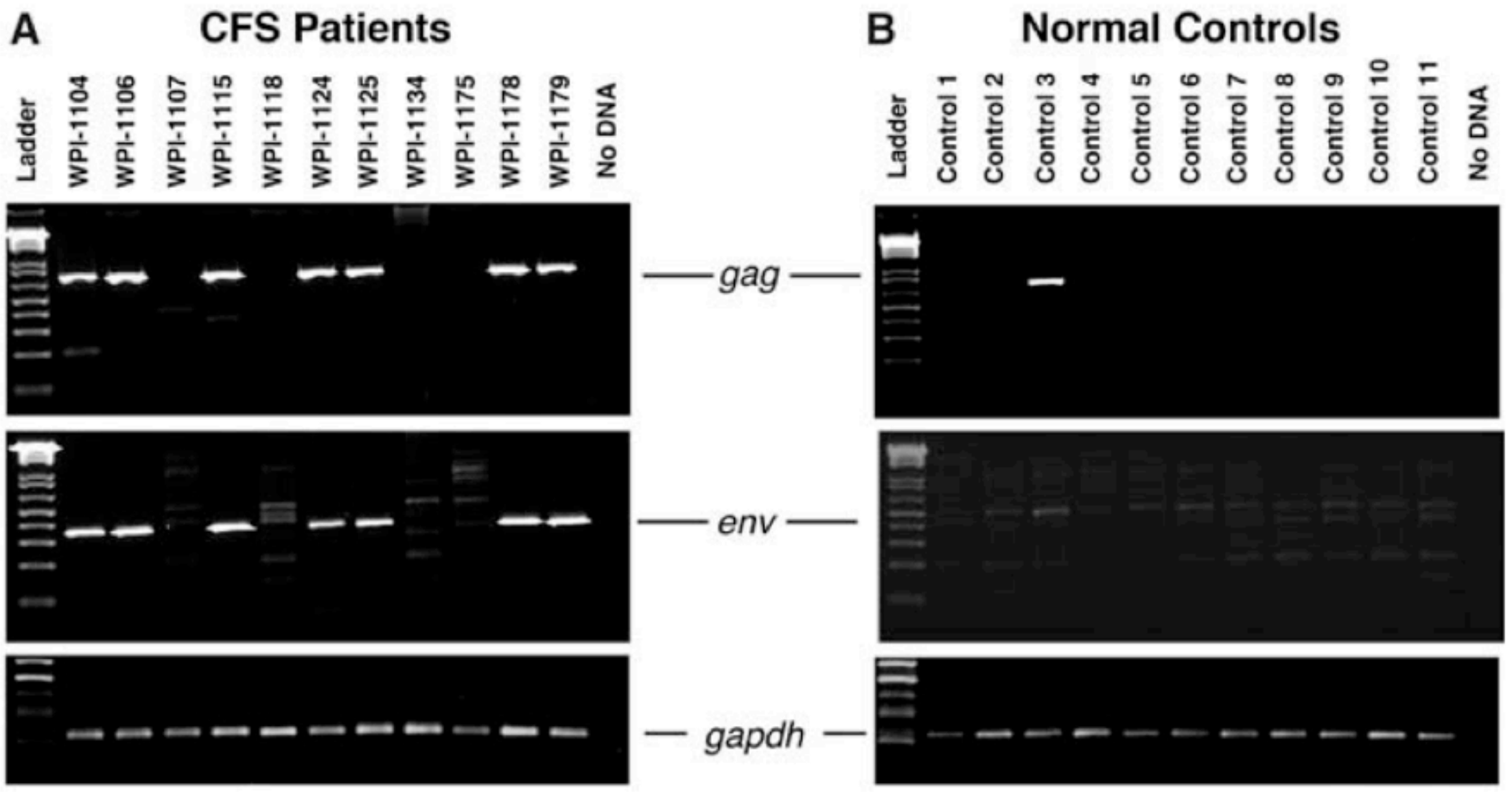



**Fig. 1.** XMRV sequences in PBMC DNA from CFS patients. Single-round PCR results for *gag*, *env*, and *gapdh* sequences in PBMCs of (**A**) CFS patients and (**B**) healthy controls are shown. The positions of the amplicons are indicated and DNA markers (ladder) are shown. These are representative results from one group of 20 patients.

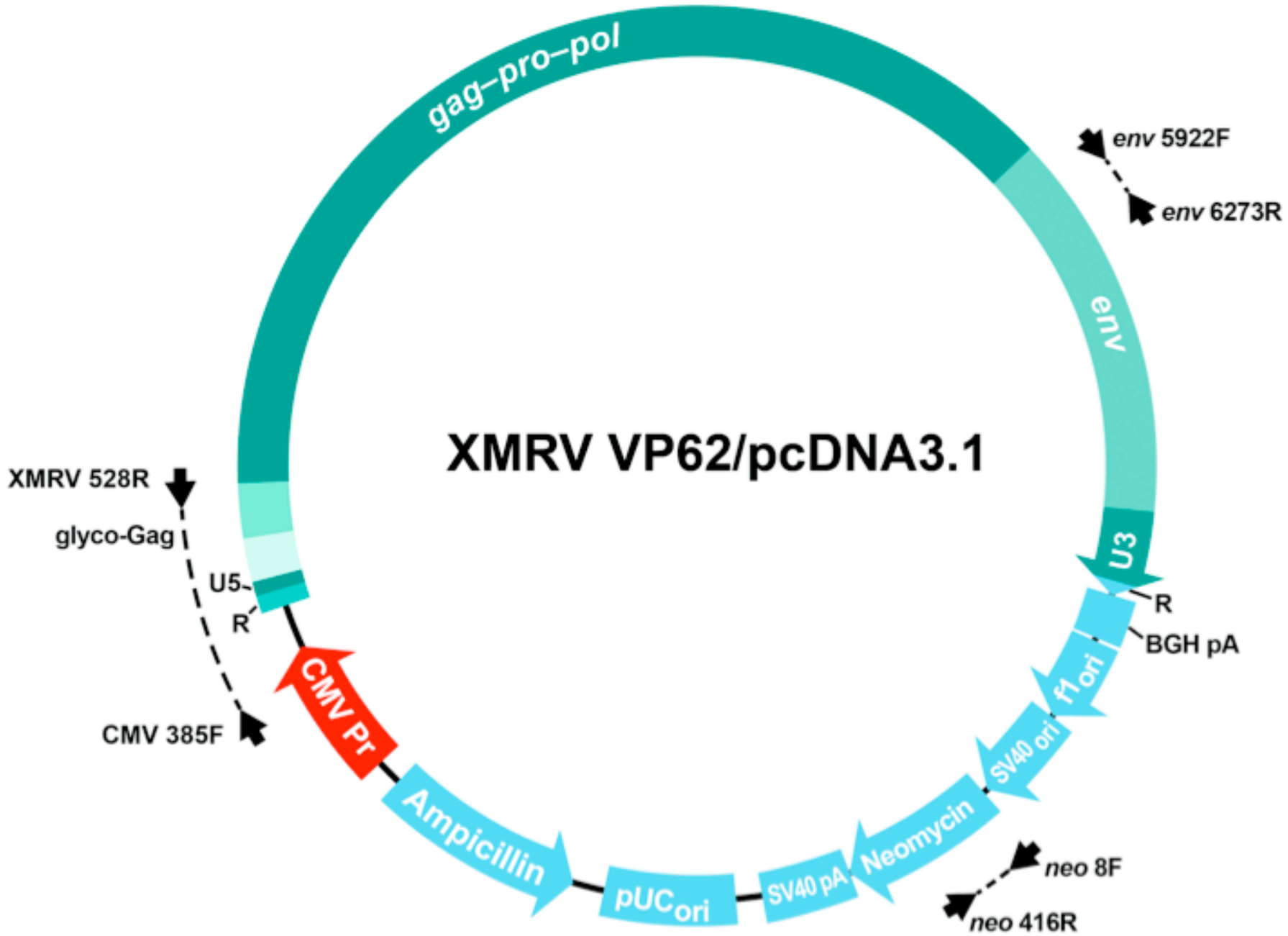
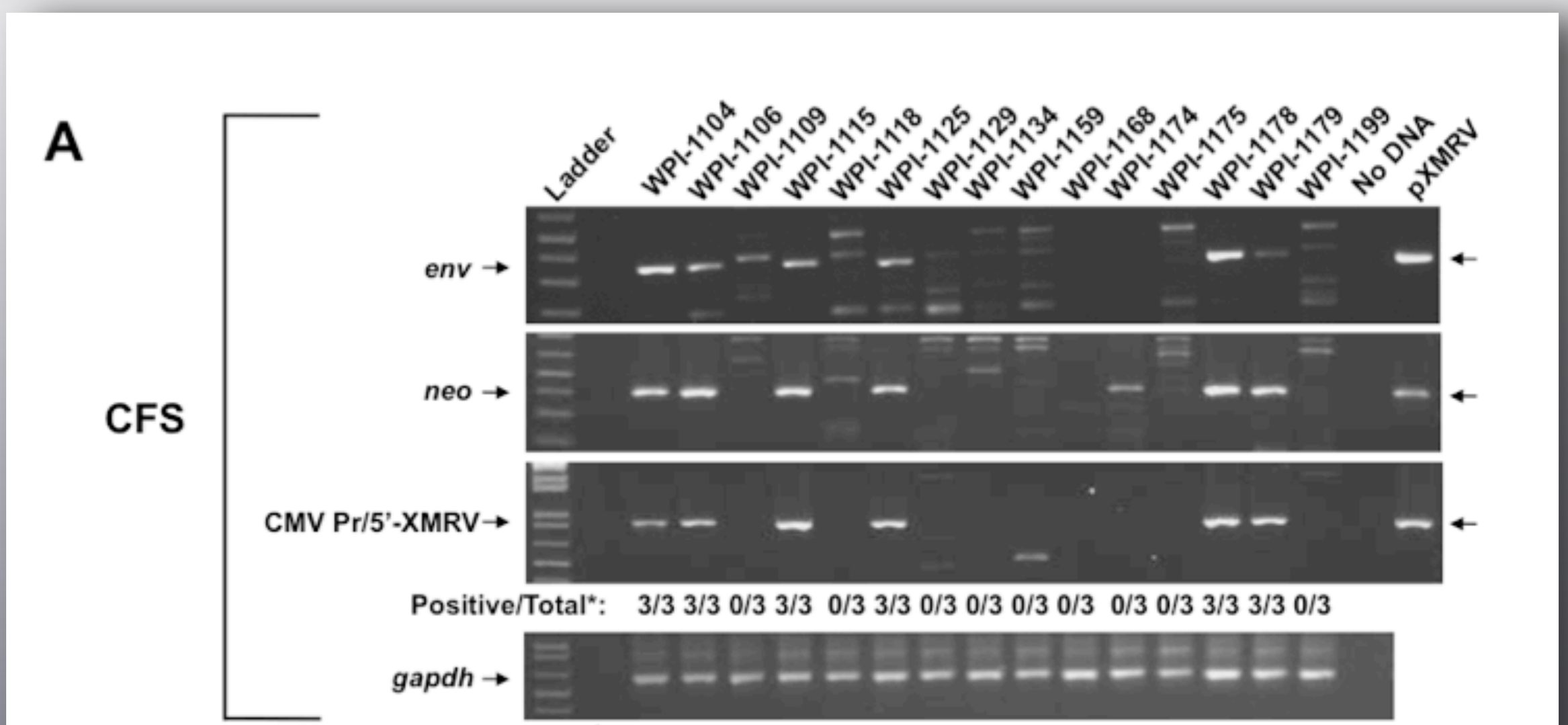

XMRV VP62/pcDNA3.1
gag–pro–pol
env
U3
R
BGH pA
f1 ori
SV40 ori
Neomycin
SV40 pA
pUC ori
Ampicillin
CMV Pr
U5
R
glyco-Gag
XMRV 528R
CMV 385F
env 5922F
env 6273R
neo 8F
neo 416R

Figure 1.


A
CFS
Ladder
WPI-1104
WPI-1106
WPI-1109
WPI-1115
WPI-1118
WPI-1125
WPI-1129
WPI-1134
WPI-1159
WPI-1168
WPI-1174
WPI-1175
WPI-1178
WPI-1179
WPI-1199
No DNA
pXMRV
env
neo
CMV Pr/5'-XMRV
Positive/Total*: 3/3 3/3 0/3 3/3 0/3 3/3 0/3 0/3 0/3 0/3 0/3 0/3 3/3 3/3 0/3
gapdh

MIS
INFORMATION
SCIENCE

Anglia Ruskin University

# 82 journals

Anglia Ruskin University

# 1.88-32.2

2009
January 2009
February 2009
April 2009
July 2009
October 2009
General Blue
2010
January 2010
February 2010
March 2010
2011
January
February
March
April
May
June
July
August
September
October
November
December

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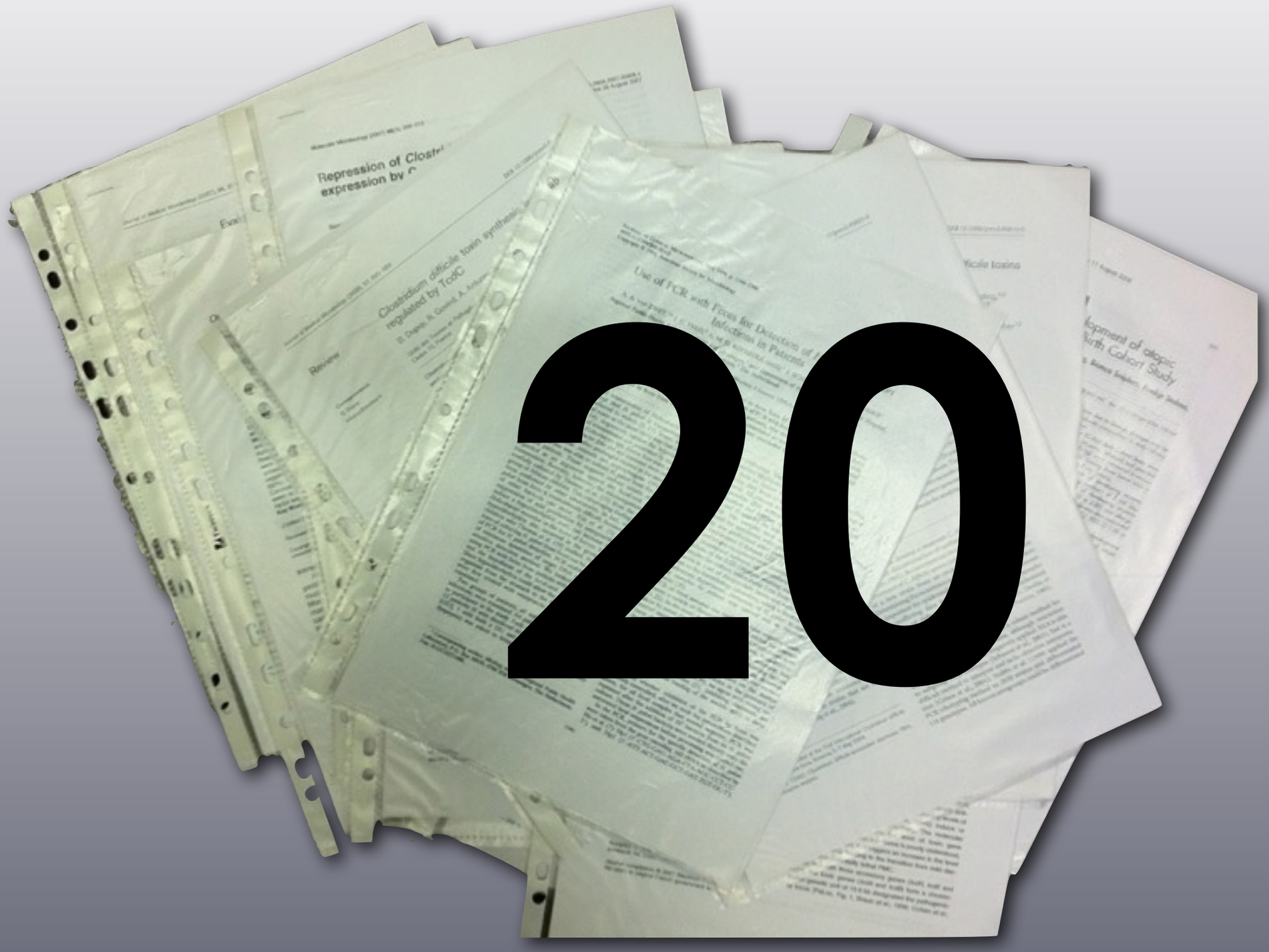

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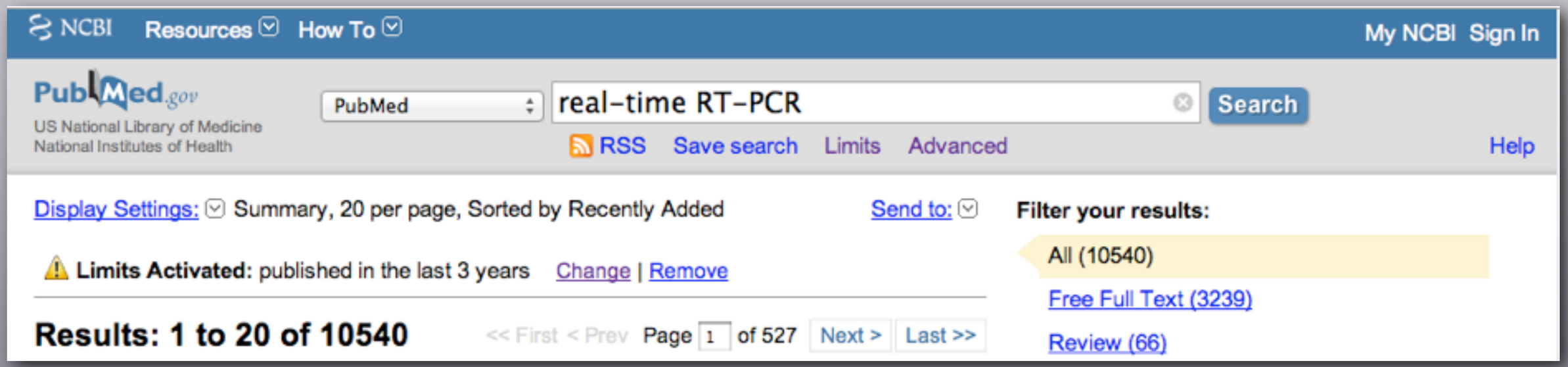
# ~1,600 papers



# Online supplements

## Developmental Biology IF 4.379

| Paper | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Online supplement | | | | | | | | | | | | | | | | | | | | |

| ✓ | ✗ |
|---|---|
| 18 | 2 |

90%

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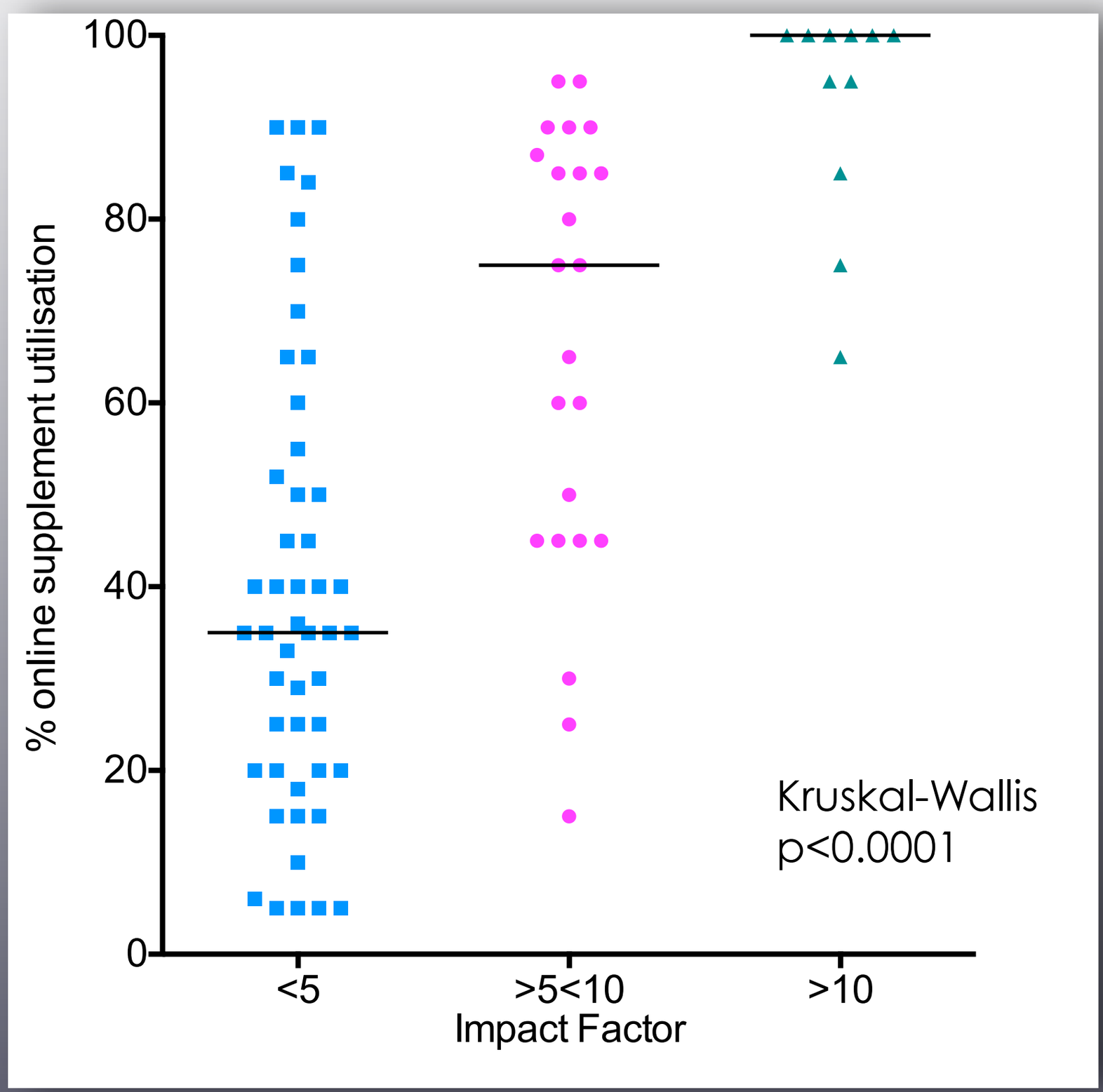
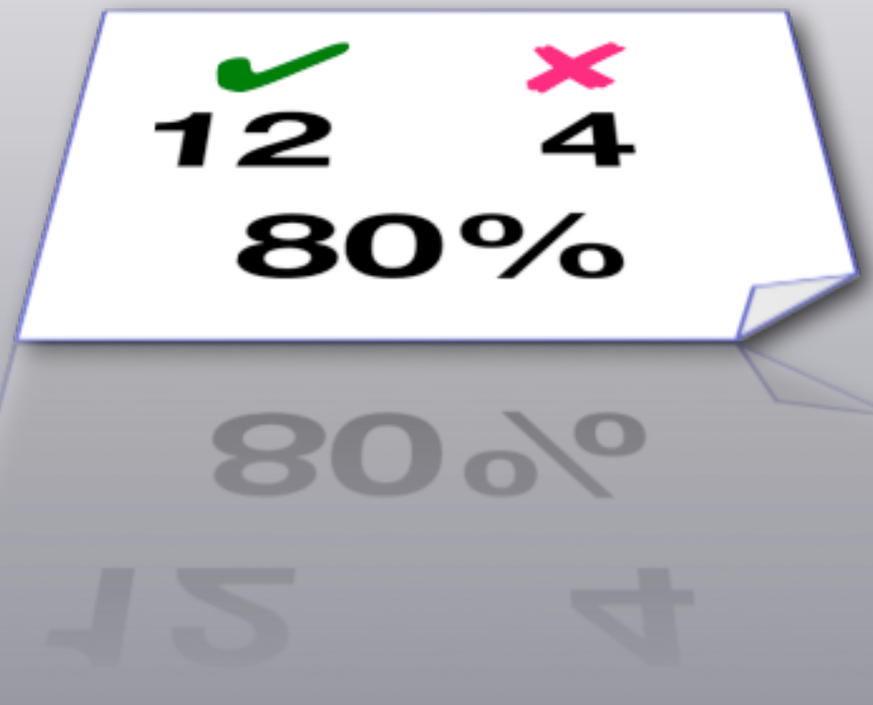
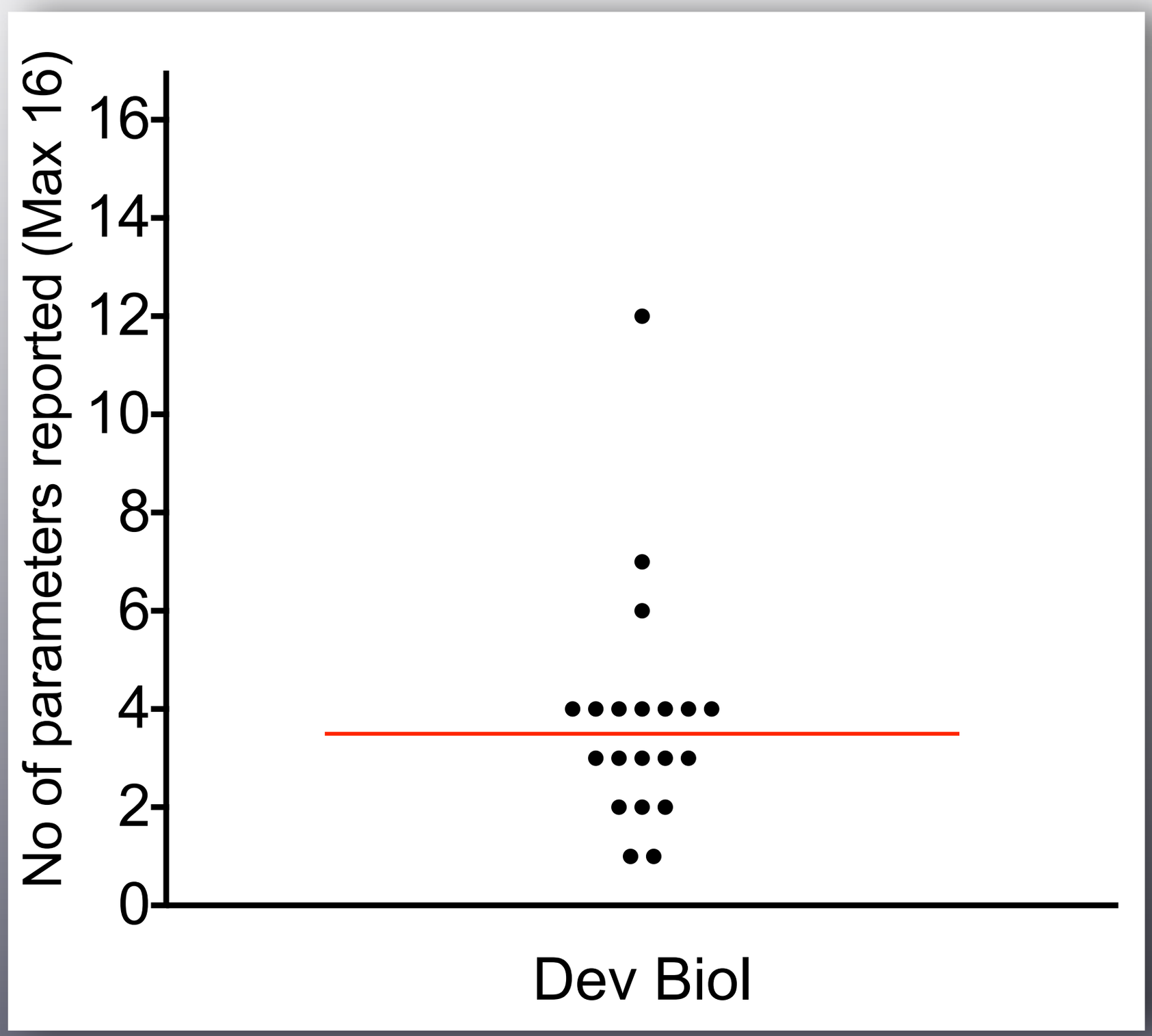
# Online supplements



| |
|---|
| **RNA quality** |
| • RNA purity |
| • RNA integrity |
| **Assay details** |
| • Target ID |
| • Primer (probe) sequences/Assay ID |
| • PCR efficiency |
| • Assay specificity |
| **Reverse transcription** |
| • input amount of RNA in RT reaction |
| • RT enzyme or RT kit |
| • priming method |
| **PCR** |
| • PCR conditions |
| • Taq polymerase or PCR kit |
| • final primer concentration |
| • input amount template in PCR reaction |
| **Normalisation** |
| • >1 reference gene (how many) |
| • reference gene validation |
| **Analysis** |
| • data-analysis method |




No of parameters reported (Max 16)
16
14
12
10
8
6
4
2
0
Dev Biol

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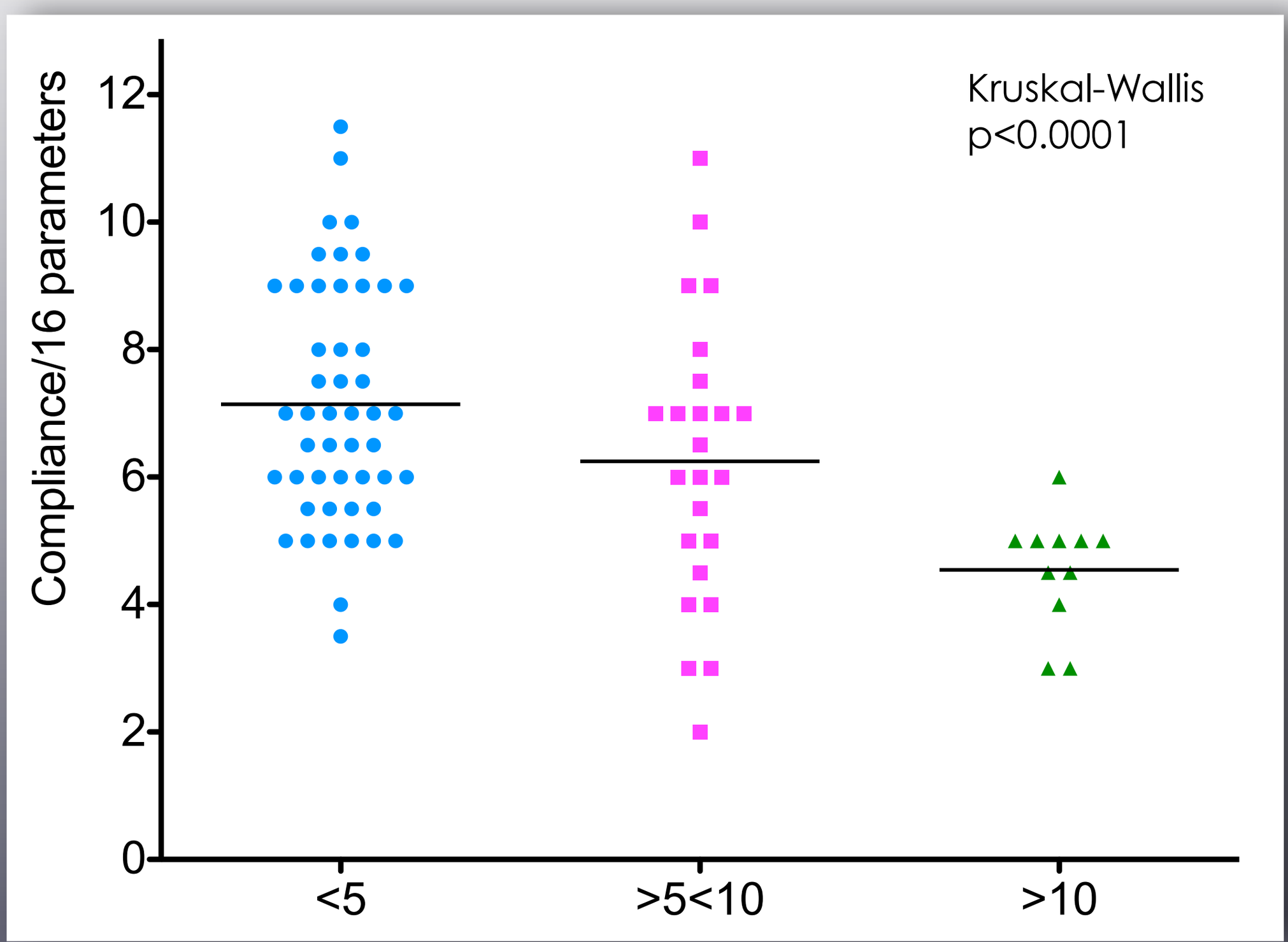
# Minimal reporting



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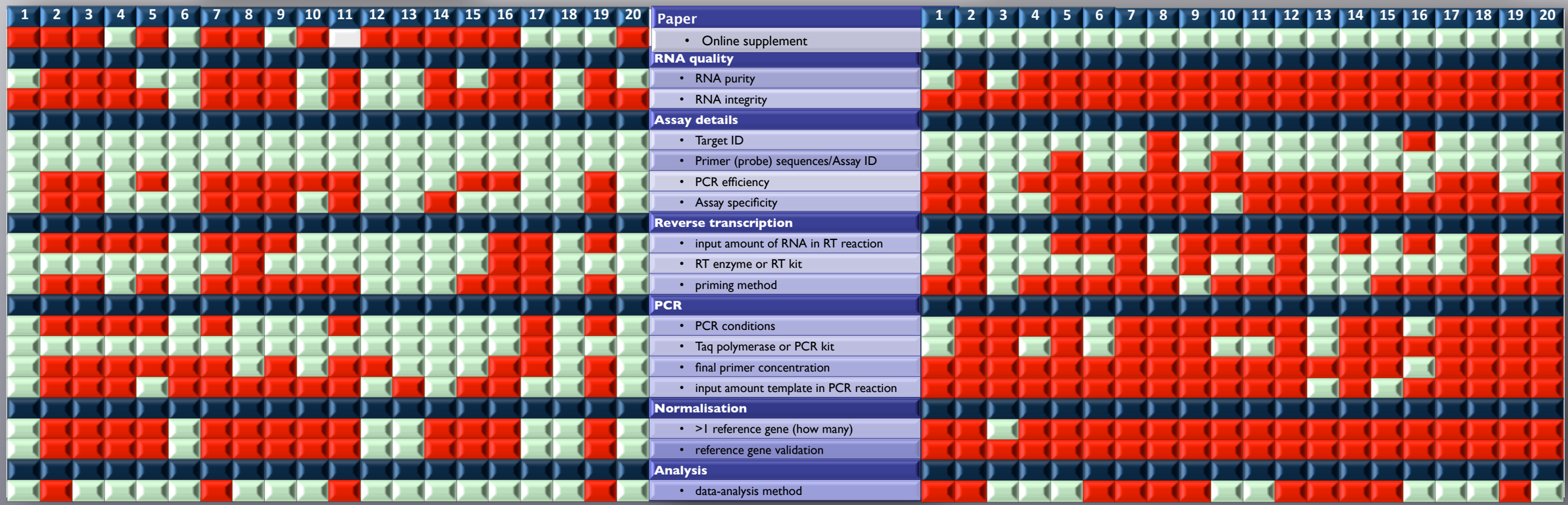
BMC Molecular Biology

nature International weekly journal of science



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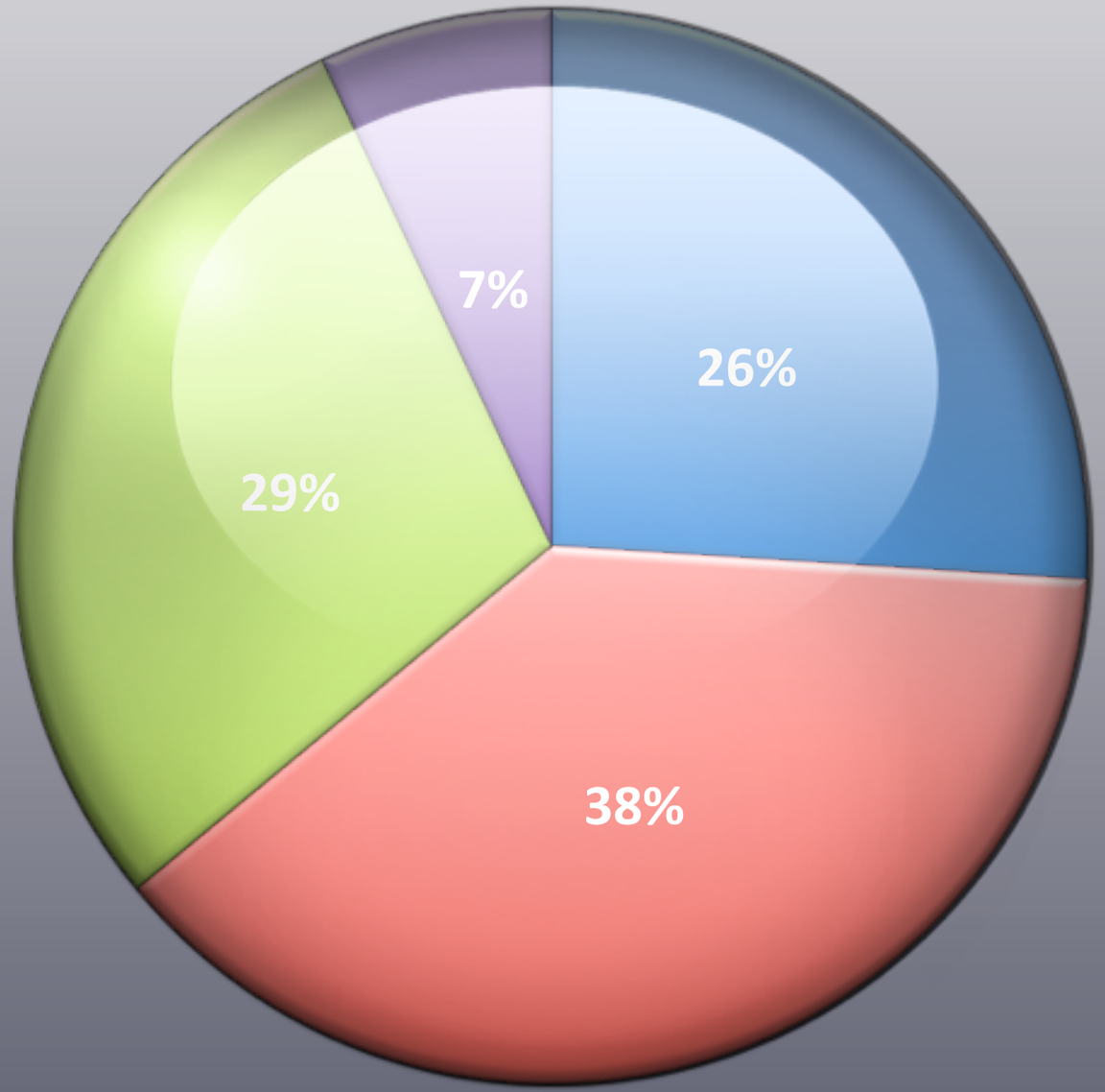
# RNA integrity

## IF<5
## % of journals with

>6/20 papers




0/20 papers

≦6/20 papers

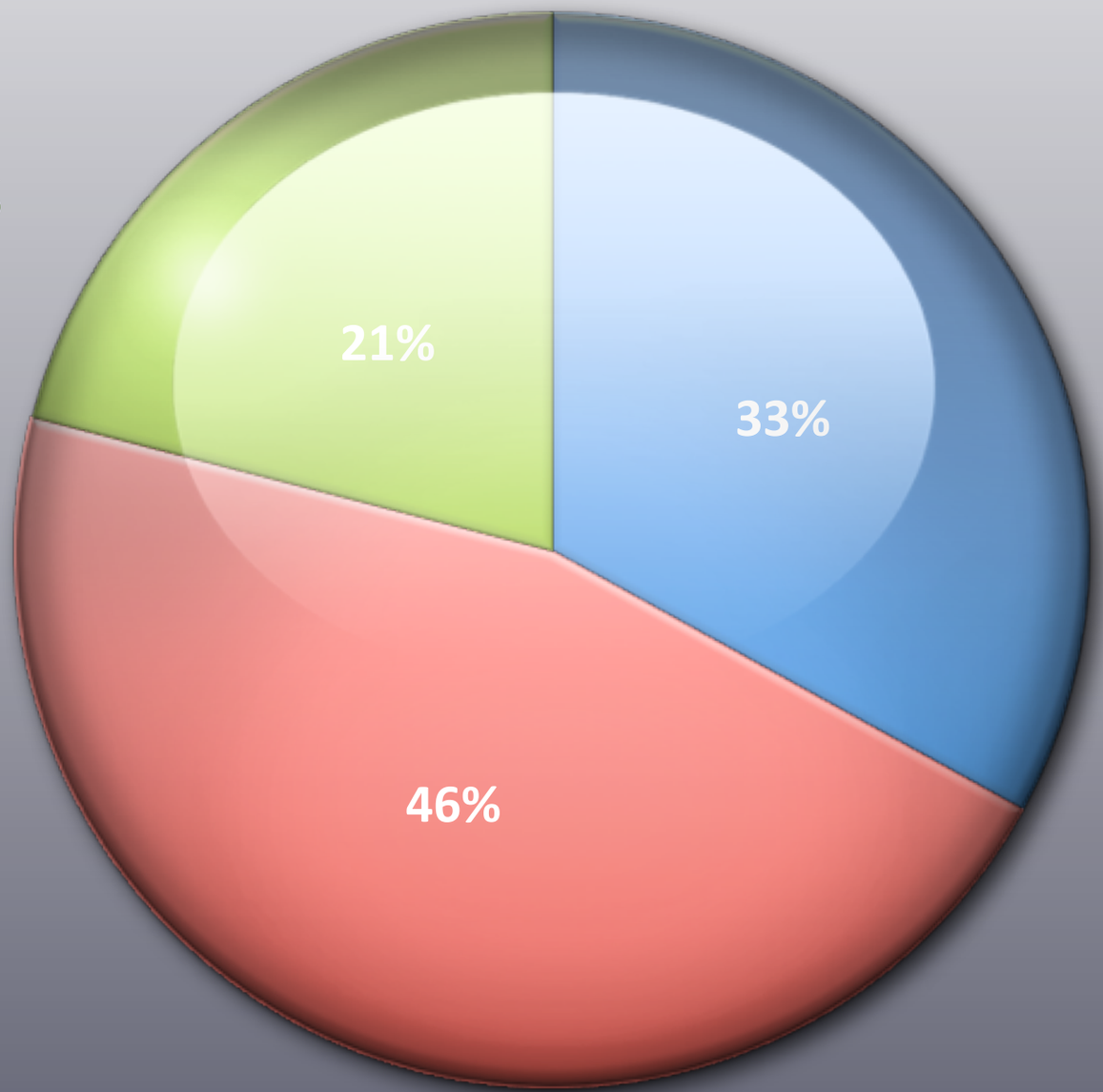
≦3/20 papers

# RNA integrity

## IF>5<10

## % of journals with

≦6/20 papers




0/20 papers

≦3/20 papers

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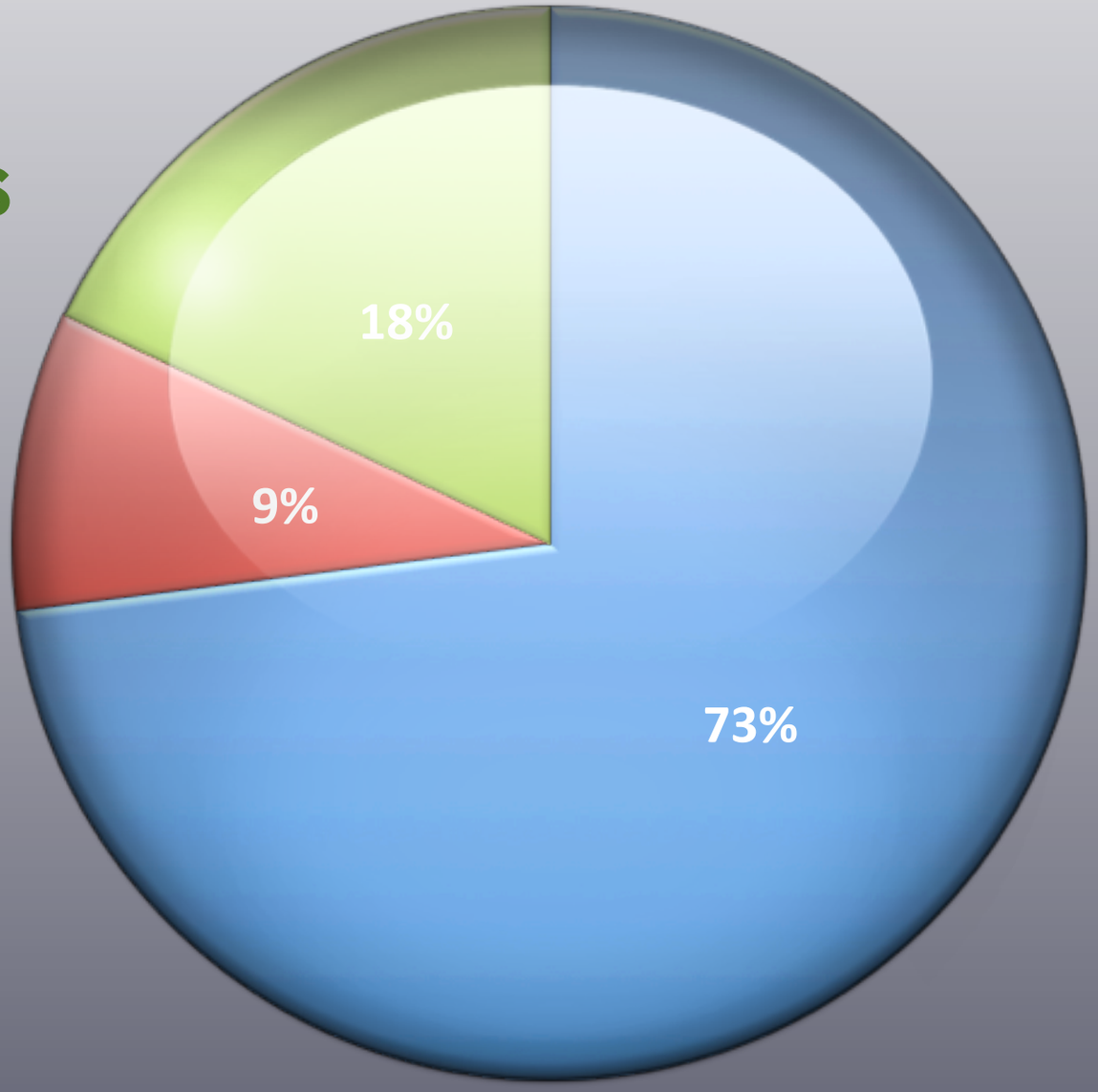
# RNA integrity

## IF>10
## % of journals with

≦6/20 papers




0/20 papers

≦3/20 papers

# Normalisation

www.tataa.com

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SCIENCE DIRECT®

Analytical Biochemistry 309 (2002) 293–300

ANALYTICAL BIOCHEMISTRY

www.academicpress.com

# Quantitative real-time reverse transcription polymerase chain reaction: normalization to rRNA or single housekeeping genes is inappropriate for human tissue biopsies☆

Carmela Tricarico,[a] Pamela Pinzani,[a] Simonetta Bianchi,[b] Milena Paglierani,[b] Vito Distante,[c] Mario Pazzagli,[a] Stephen A. Bustin,[d,*] and Claudio Orlando[a]

[a] *Clinical Biochemistry Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy*
[b] *Department of Human Pathology and Oncology, University of Florence, Florence, Italy*
[c] *Department of Surgery, University of Florence, Florence, Italy*
[d] *Academic Department of Surgery, Barts and the London, Queen Mary's School of Medicine and Dentistry, 4th Floor Alexandra Wing, Royal London Hospital, University of London, London E1 1BB, UK*

Received 11 June 2002

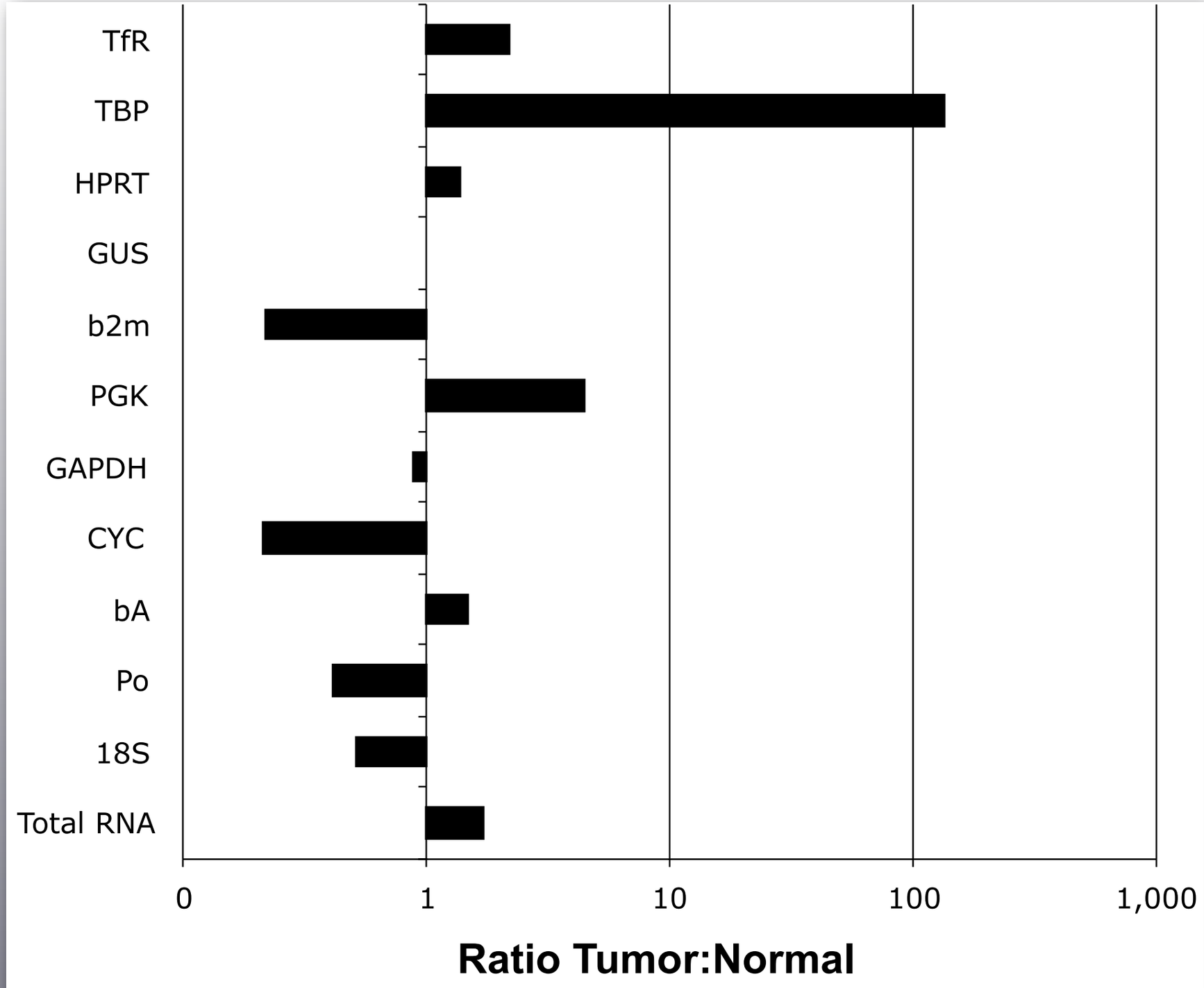
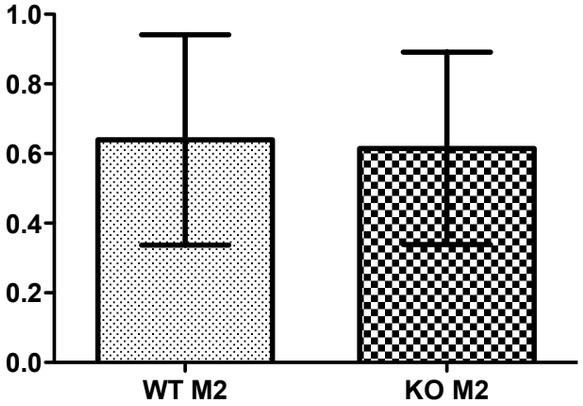
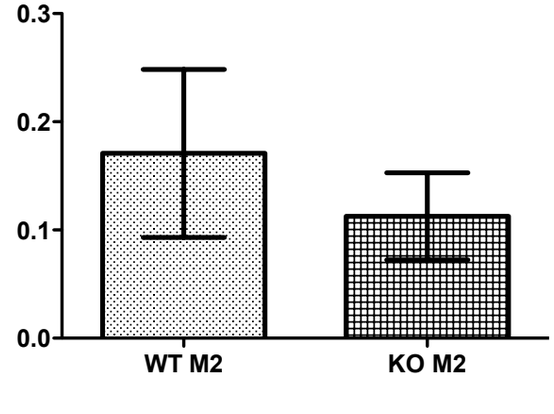
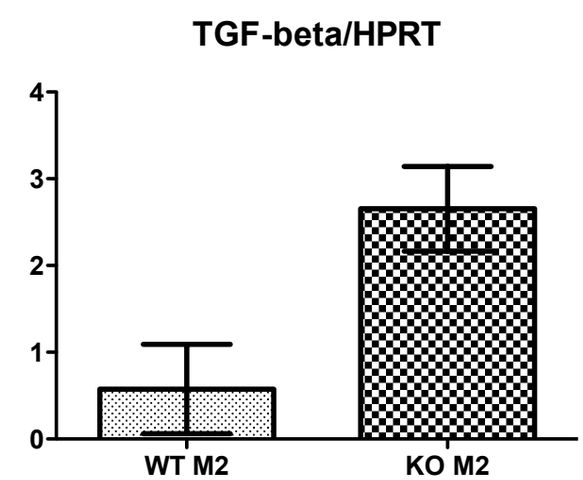
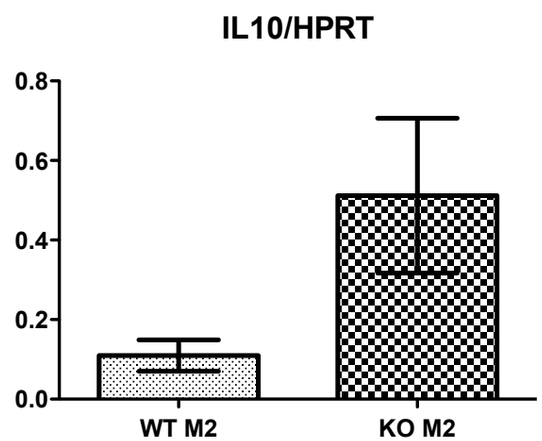


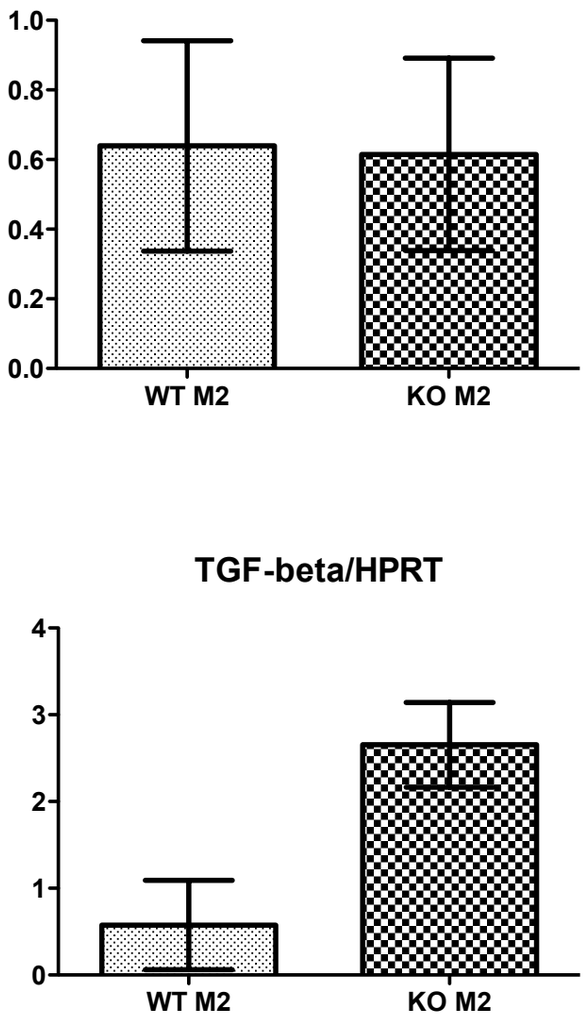

Fig. 5. Comparison of normalization to total RNA or to 11 endogenous control genes in one patient. The Tumor:Normal ration was calculated as (Tumor VEGF copy number, normalized to total RNA or individual endogenous control RNA)/(Paired normal VEGF copy number, normalized to total RNA or individual endogenous control RNA).

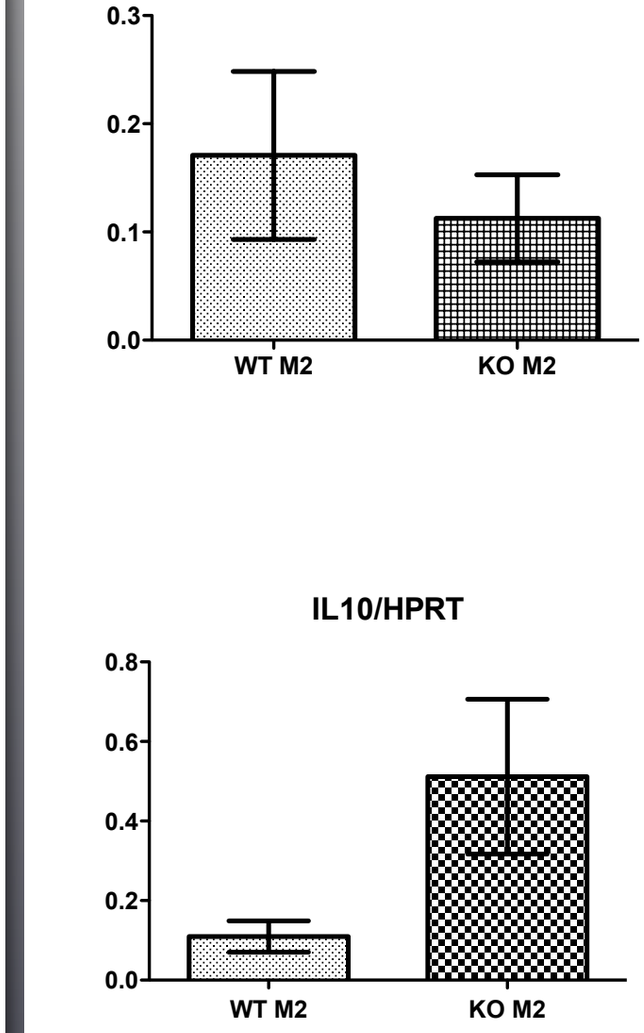

TGF-beta/cyclophilin
1.0
0.8
0.6
0.4
0.2
0.0
WT M2
KO M2

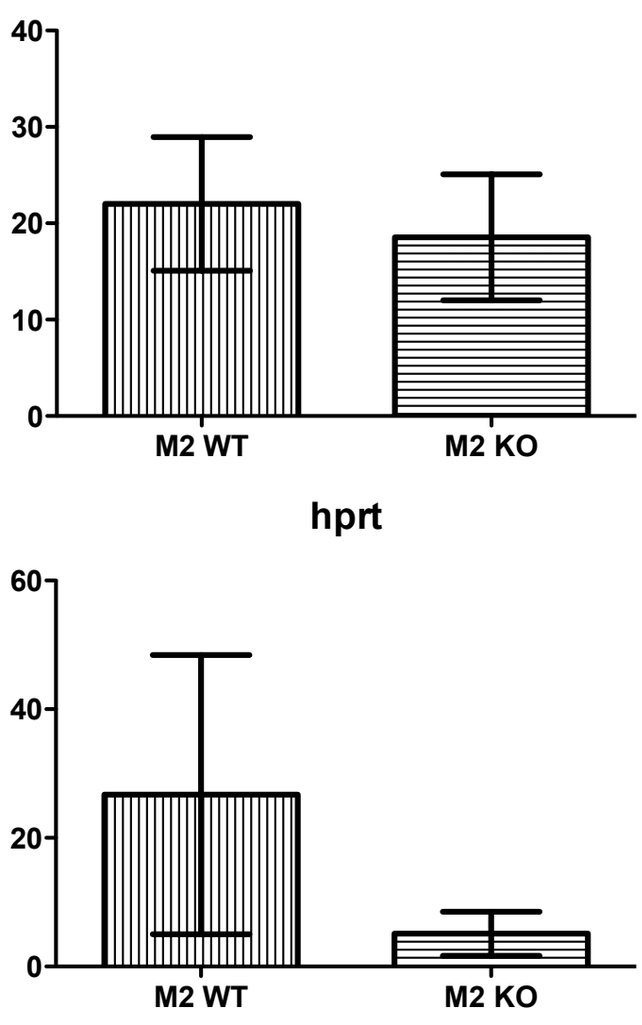

IL10/cyclophilin
0.3
0.2
0.1
0.0
WT M2
KO M2


TGF-beta/HPRT
4
3
2
1
0
WT M2
KO M2


IL10/HPRT
0.8
0.6
0.4
0.2
0.0
WT M2
KO M2


TGF-beta/cyclophilin
1.0
0.8
0.6
0.4
0.2
0.0
WT M2
KO M2
TGF-beta/HPRT
4
3
2
1
0
WT M2
KO M2


IL10/cyclophilin
0.3
0.2
0.1
0.0
WT M2
KO M2
IL10/HPRT
0.8
0.6
0.4
0.2
0.0
WT M2
KO M2


cyclophilin
40
30
20
10
0
M2 WT
M2 KO
hprt
60
40
20
0
M2 WT
M2 KO

# Reference genes

## Developmental Biology IF 4.379

| Paper | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| • >1 RG (how many) | | | 2 | | 2 | | 2 | | | | | | | | | | | | | |
| • RG validation | | | | | | | | | | | | | | | | | | | | |

✓ 3 ✗ 17

✓ 1 ✗ 19

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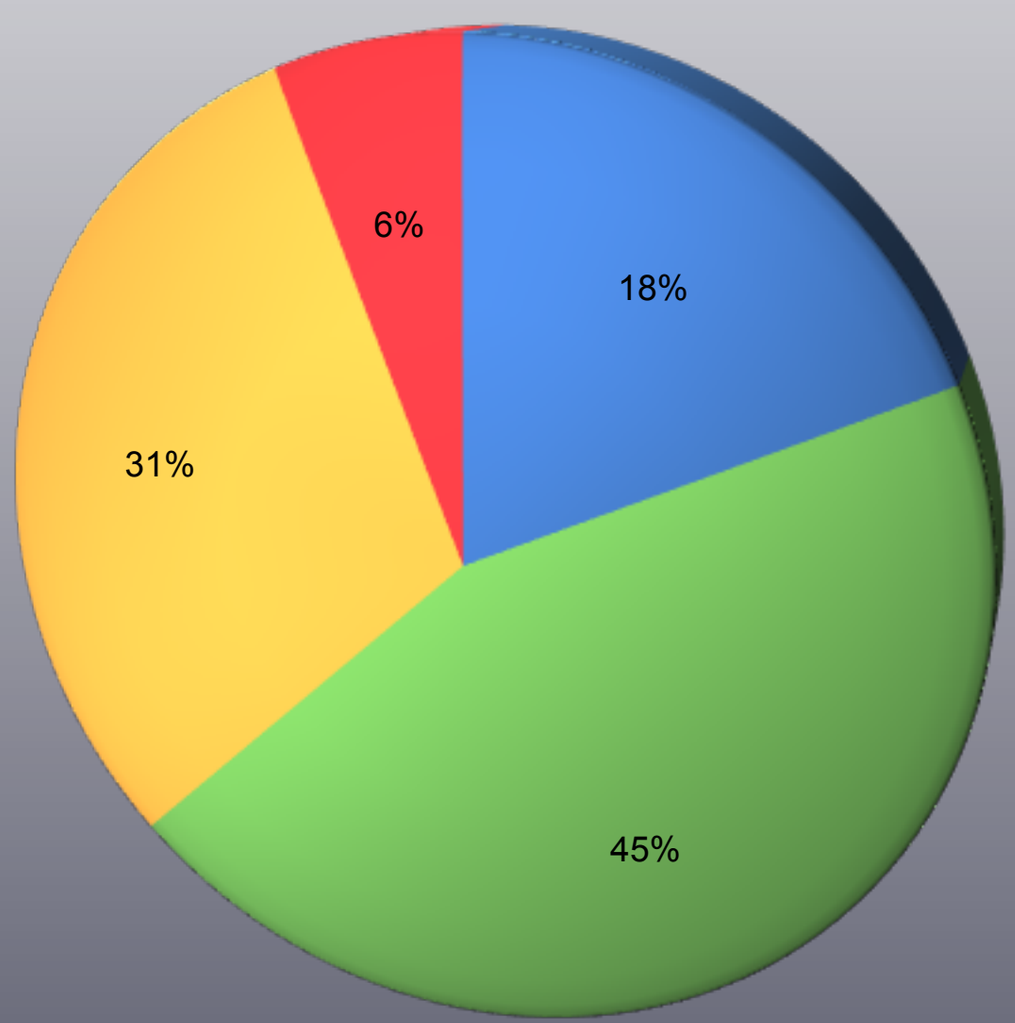
# Use of >1RG

## % of journals with

>6/20 papers

0/20 papers




≦6/20 papers

≦3/20 papers

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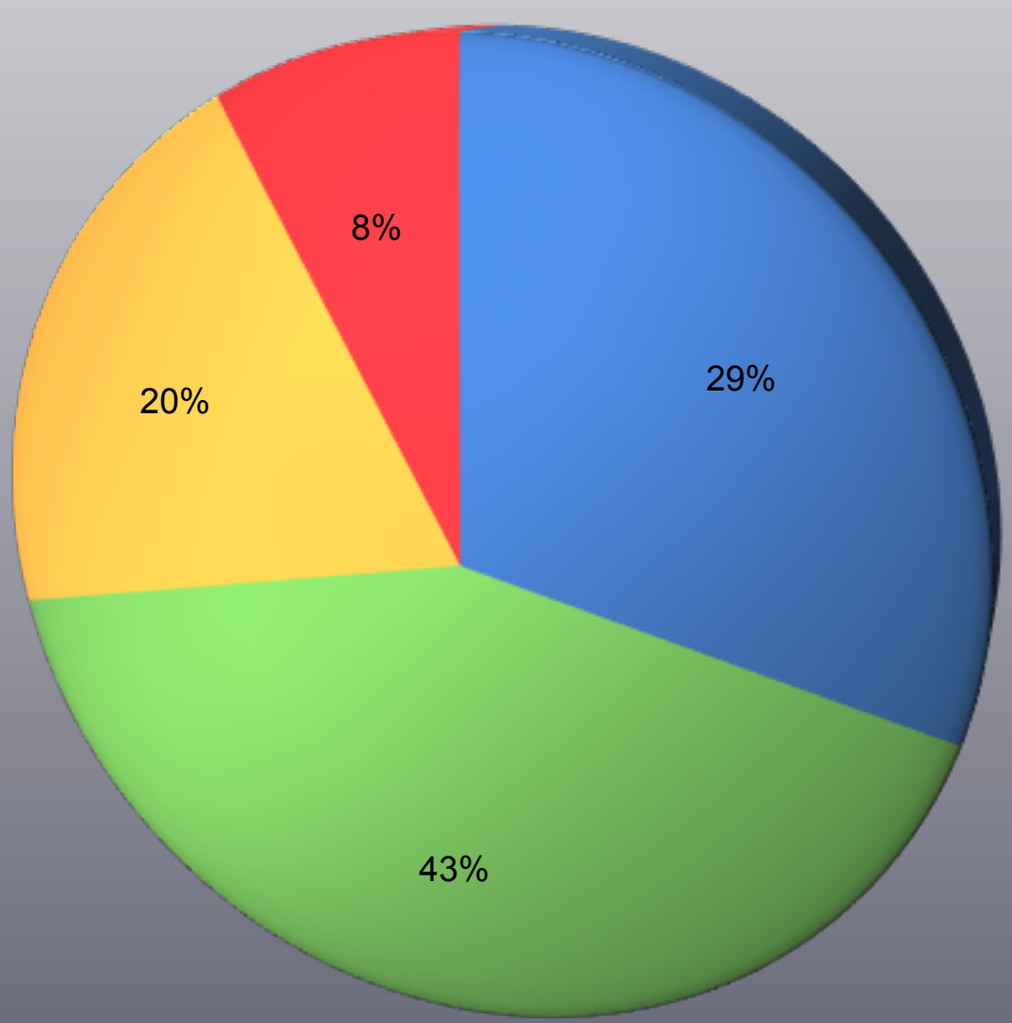
# Validated RG IF<5

## % of journals with

>6/20 papers

0/20 papers




≦6/20 papers

≦3/20 papers

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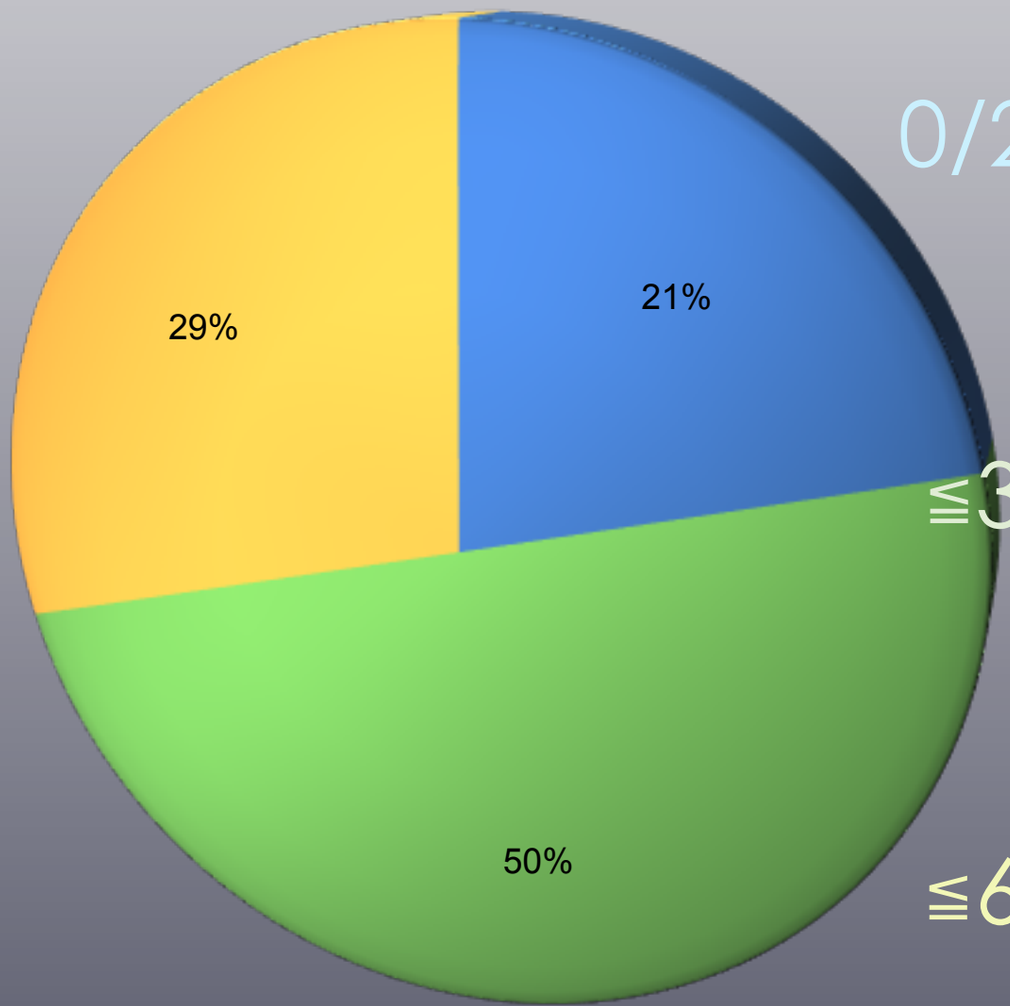
# >1 Reference gene

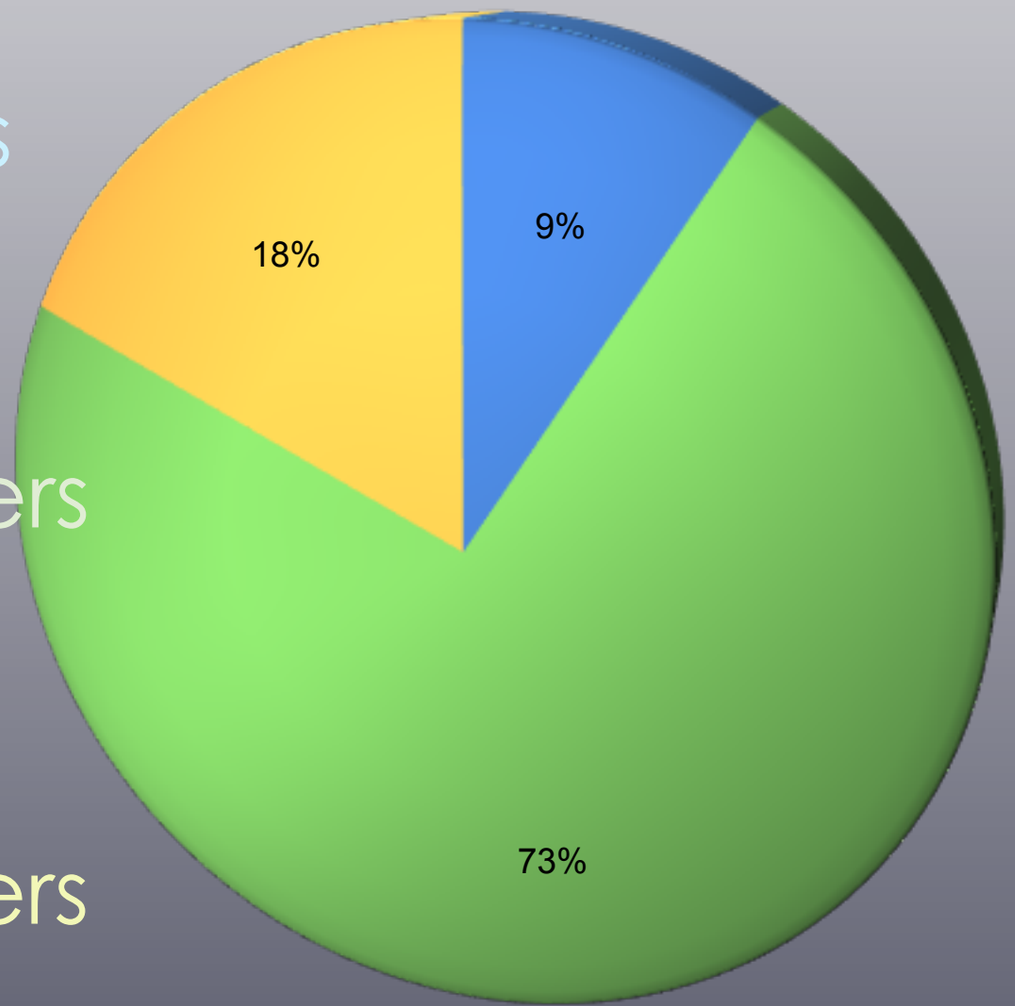
## IF>5<10

## IF>10

% of journals with




0/20 papers




≦3/20 papers

≦6/20 papers

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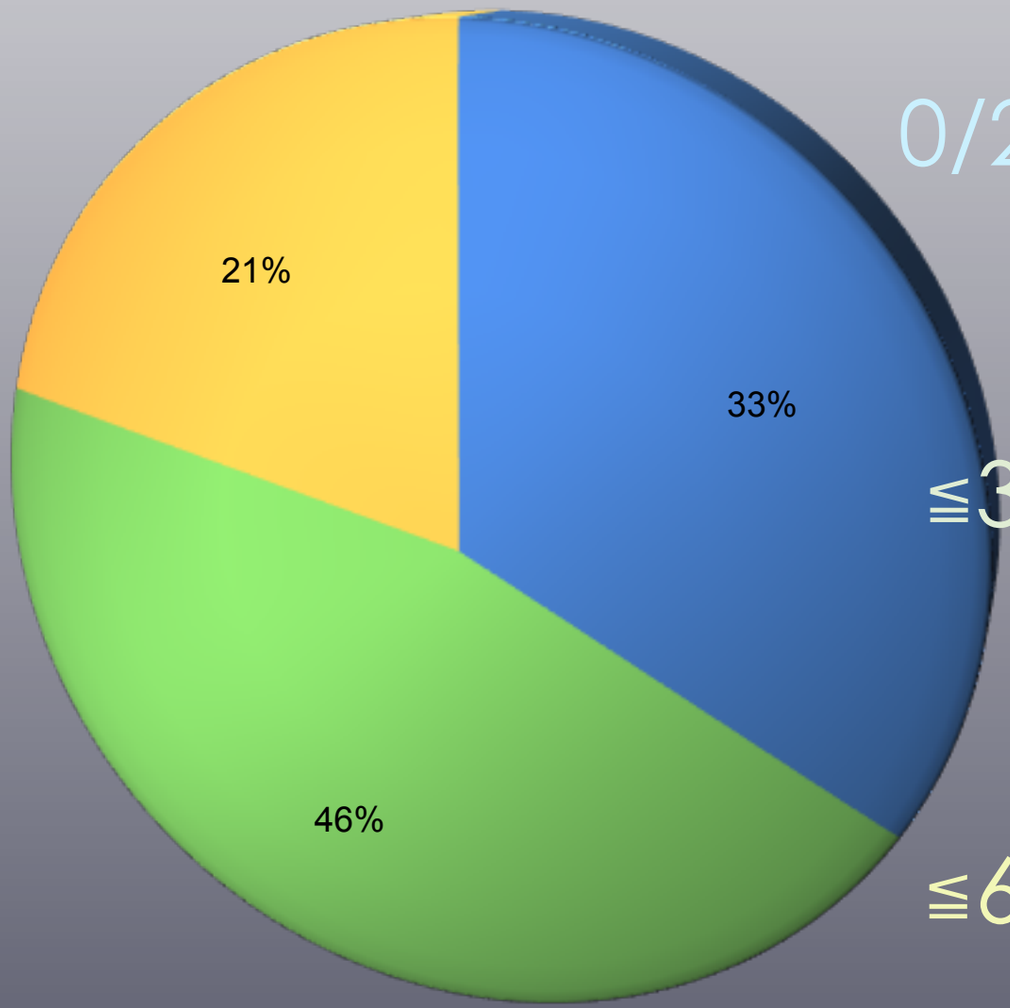
# Validated RG

## IF>5<10

## IF>10

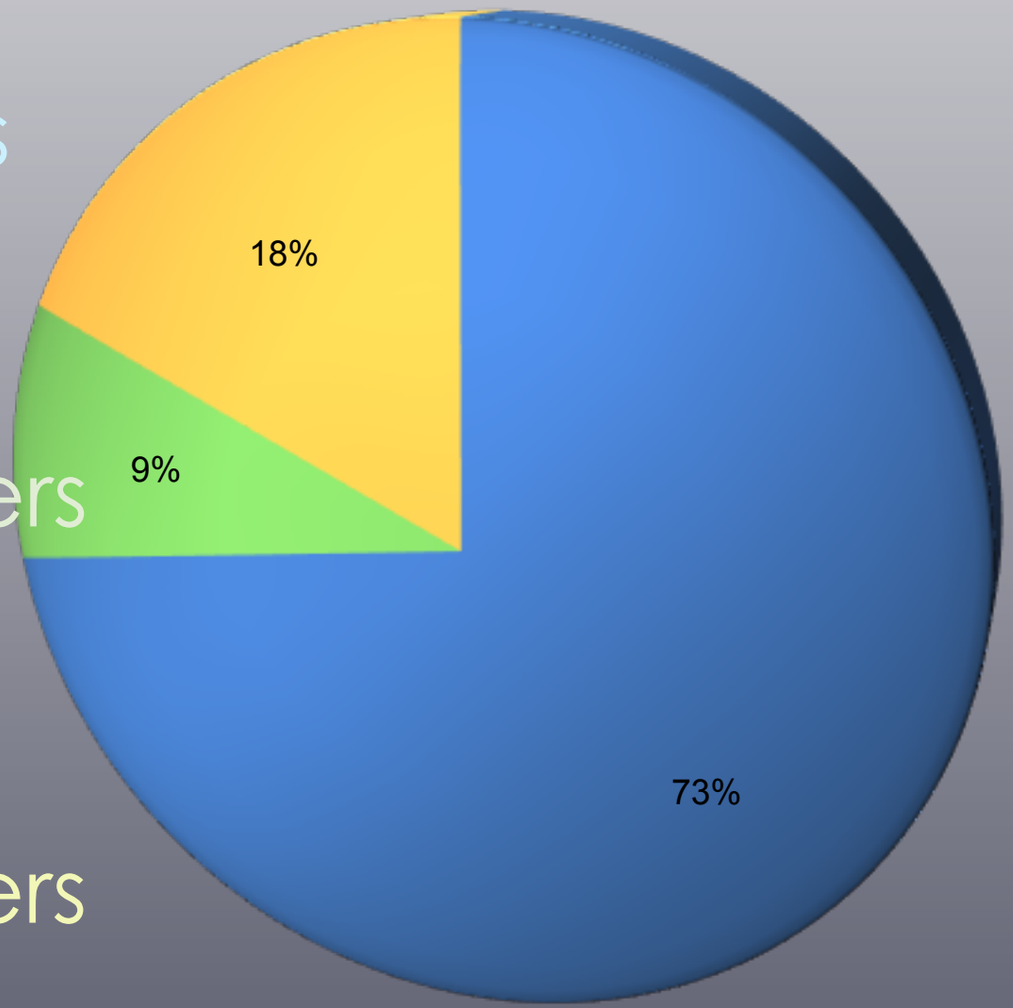
% of journals with

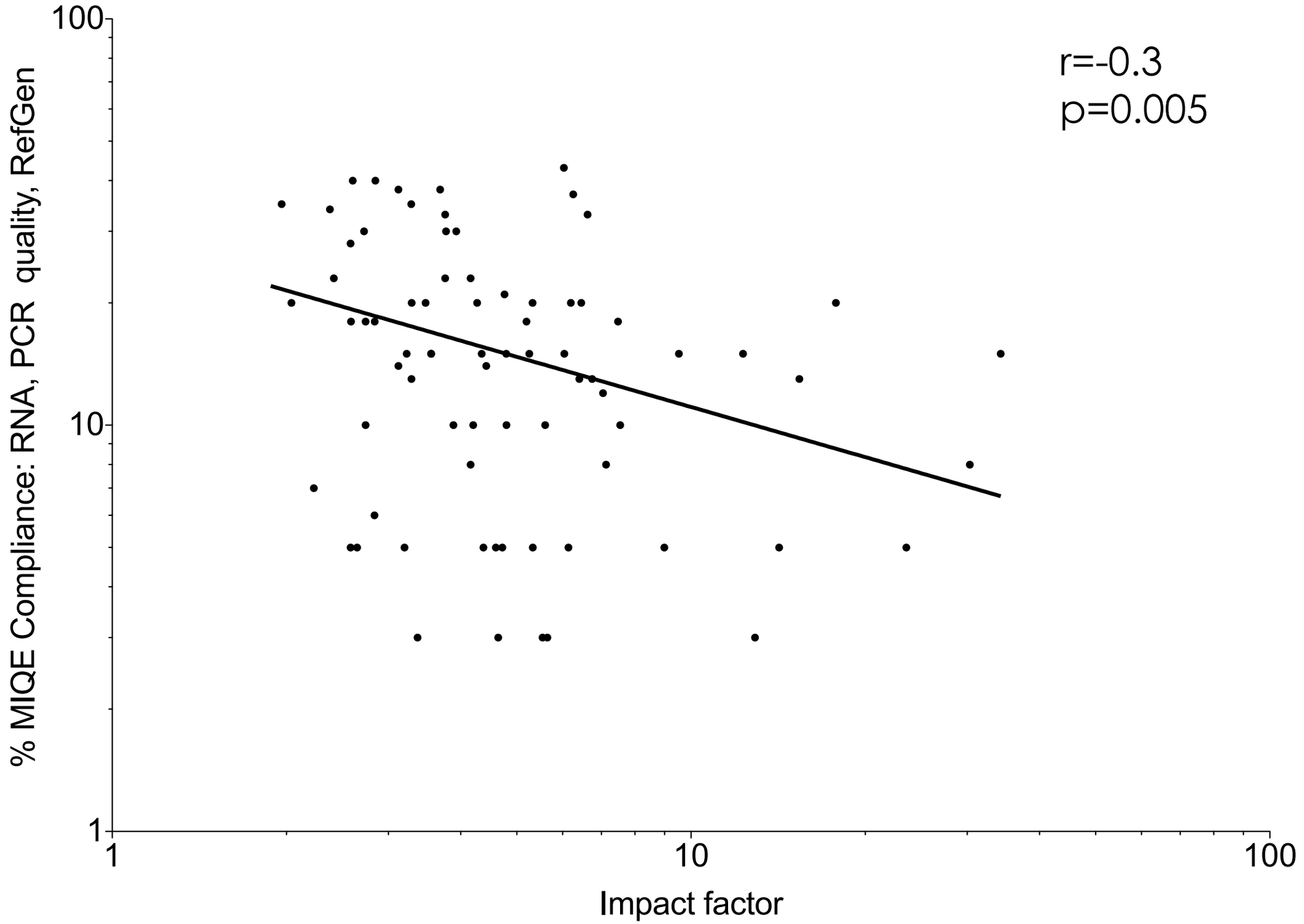



0/20 papers

≦3/20 papers

≦6/20 papers




r=-0.3
p=0.005
% MIQE Compliance: RNA, PCR quality, RefGen
Impact factor
100
10
1
1
10
100

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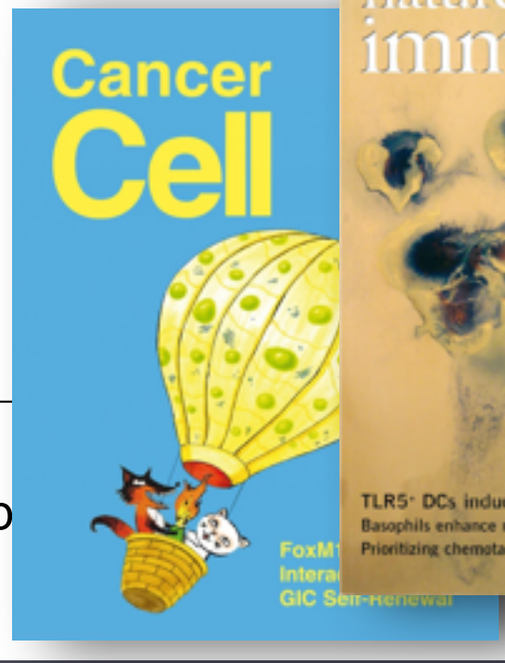
BMC Molecular Biology

IMPACT FACTOR 3.19

r=-0.3
p=0.005



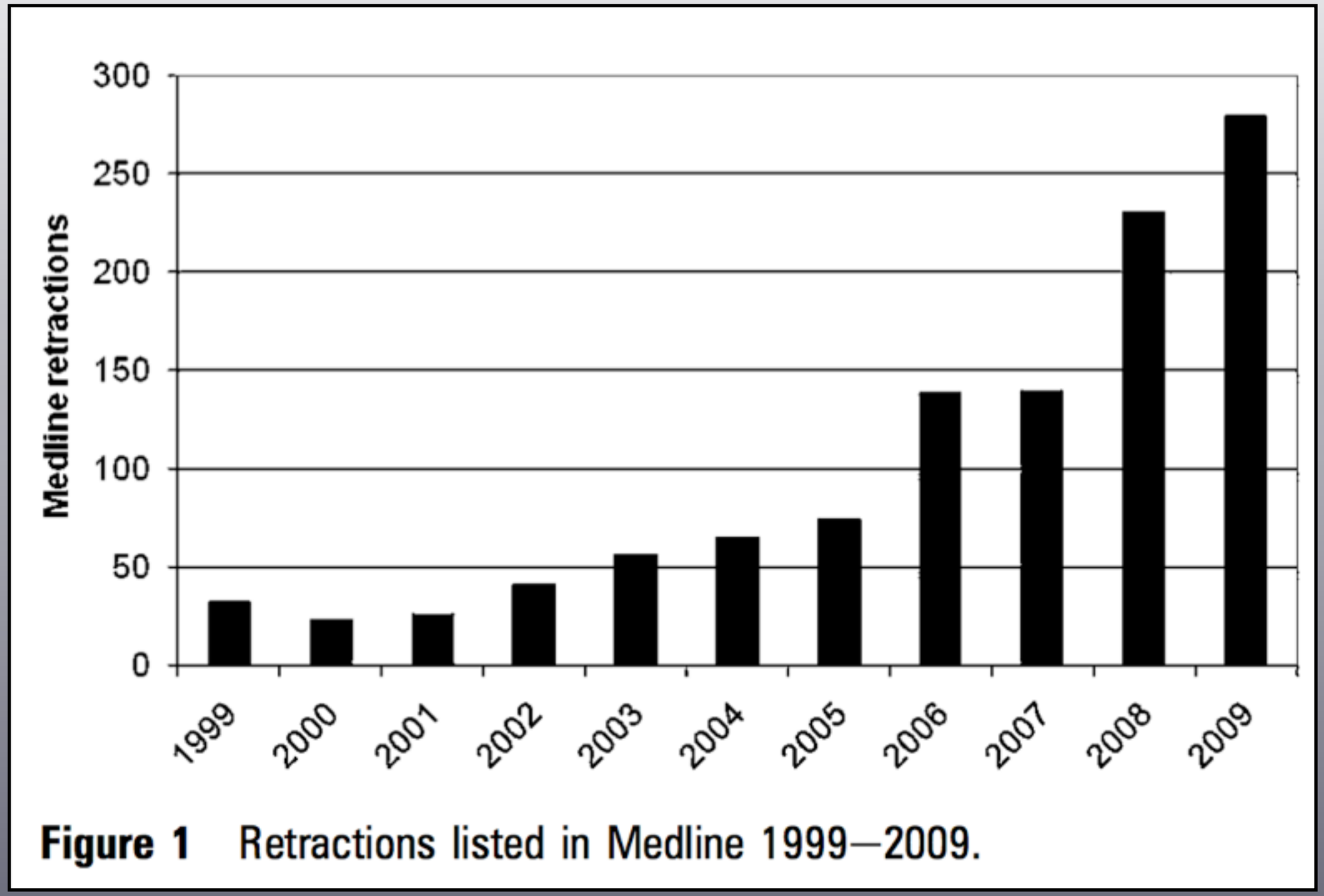
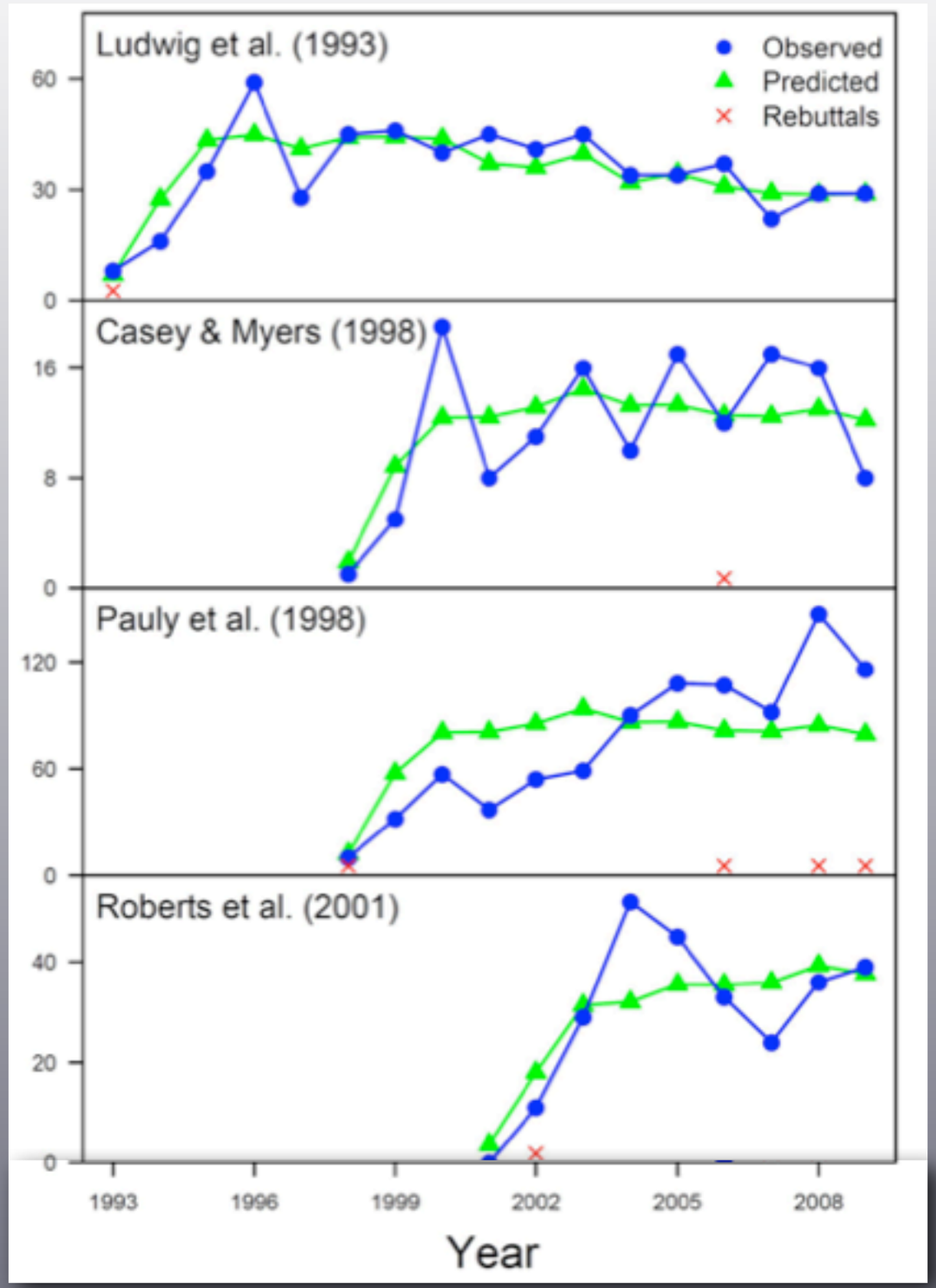
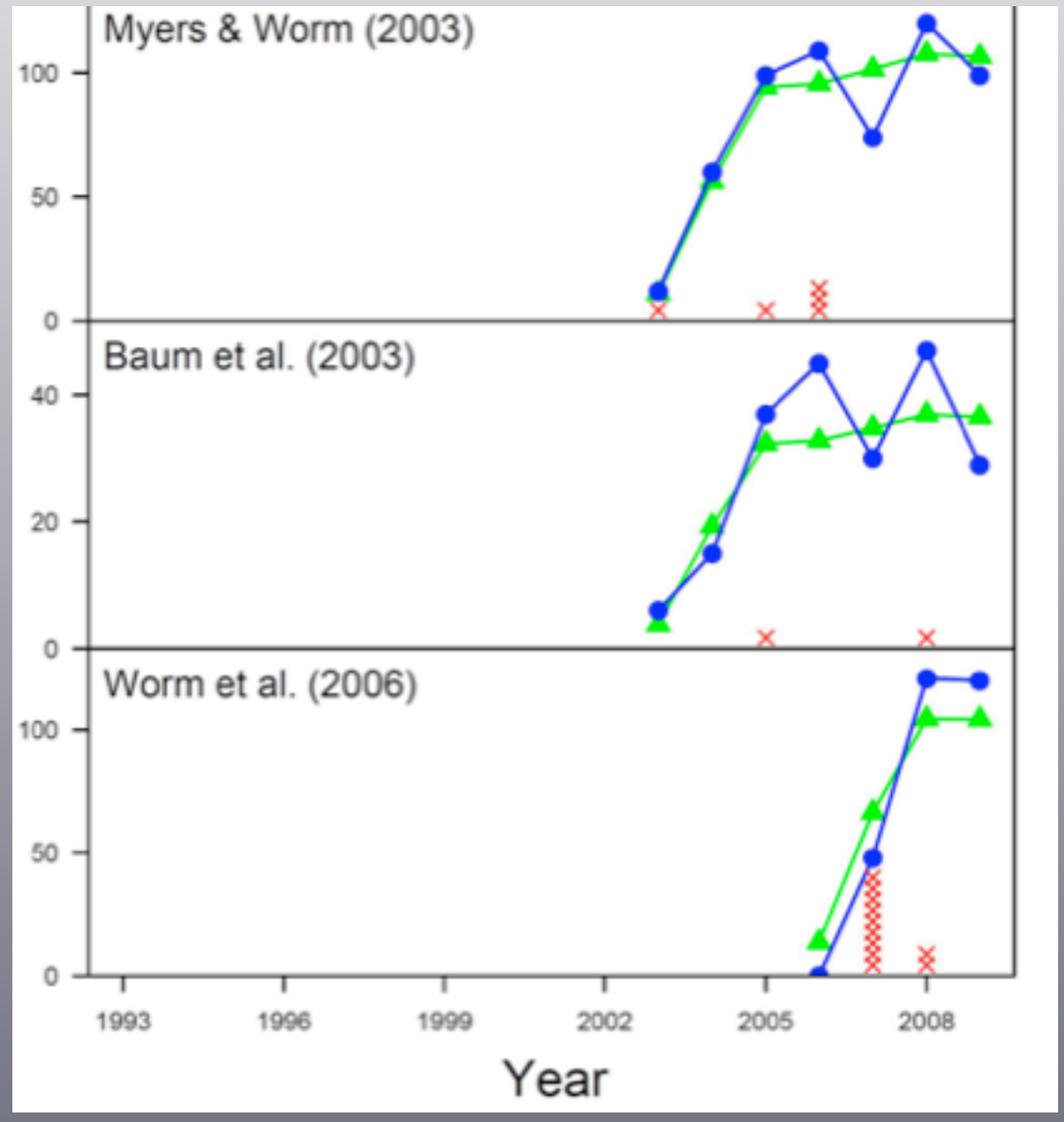



**Figure 1** Retractions listed in Medline 1999—2009.

Wager & Williams *J Med Ethics* (2011)



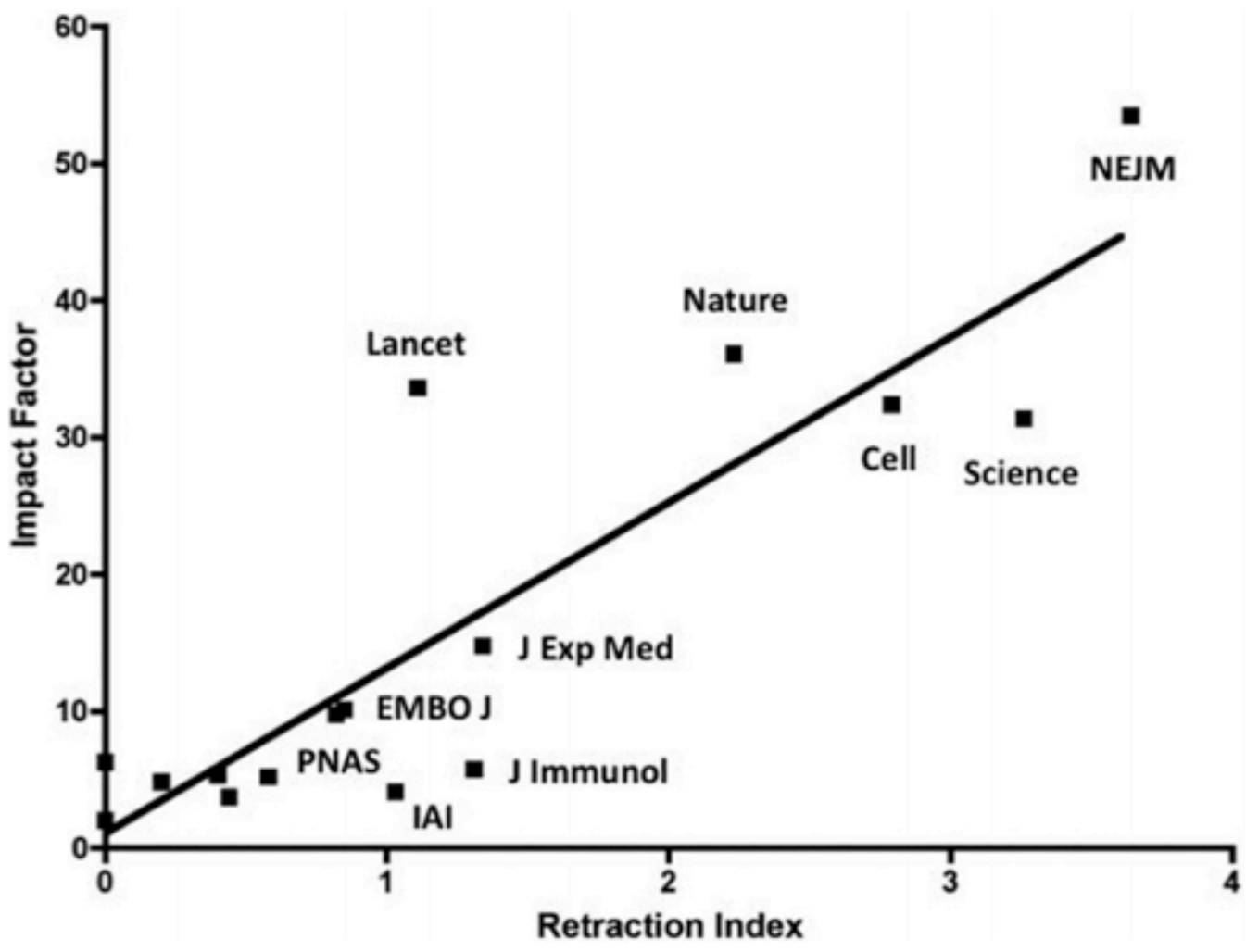

Banobi et al *Ecosphere* (2011)

**Table 1** Summary of reasons for retraction of 742 papers, 2000–10

| Reason for retraction | Retracted papers, n (%) | IF, mean (SD) |
|---|---|---|
| Fraud | | |
| Fabrication | 111 (15.0) | 9.79 (11.49) |
| Falsification | 98 (13.2) | 8.01 (8.33) |
| Error | | |
| Scientific mistake | 234 (31.5) | 10.60 (10.66) |
| Duplicate publication | 117 (15.8) | 3.18 (2.63) |
| Plagiarism | 107 (14.4) | 2.31 (1.90) |
| Ethical violations | 76 (10.2) | 5.74 (8.51) |
| Unstated reasons | 61 (8.2) | 5.08 (8.82) |
| Journal error | 27 (3.6) | 2.66 (2.21) |

IF, impact factor.

Steen *J Med Ethics* (2010)




Fang & Casadevall *Infection and Immunity* (2011)

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# Summary

- Scientific short cuts, error and deception are common
- Molecular techniques are not reliable
- The scientific literature is littered with false conclusions

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# Conclusions

- The public are right to be skeptical about scientific/ medical research
- There is an urgent need for transparancy

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# Survey

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Jeremy Garson
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Joni Van der Meulen
Joris Wauman
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Karen Goossens
Karen Smeets
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Kato Deckers
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Michelle Plusquin
Mireille Van Gele
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Stephanie Coulon
Tania Nolan
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Tim Van Acker
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Pieter Rondou
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Sara Zaccara
Sarah Vergult
Sofia Morais