# Real Impediments to Academic Biomedical Research

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Presentation to CASIMIR Workshop, Rome
May 21, 2009

This research was funded by the National Academy of Sciences, Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions of the National Academies' Board on Science, Technology, and Economic Policy and Program on Science, Technology and Law.

# Changing Context of Academic Biomedical Research

- Increasing commercialization of environment for academic biomedical research
  - More commercial activity by universities
  - More patents on inputs to university research

# Privatization of the biomedical "scientific commons"

- The conventional question:
  - Is the patenting of upstream discoveries conferring upon academics and their institutions both the means and incentive to exclude other academics from using research and material inputs to subsequent research?

# Suggestions

- Broaden the object of analysis beyond patent-protected knowledge
- Consider the flows of research inputs more generally
- **And consider the private costs and benefits of exclusionary behavior, and what drives those costs and benefits**

# What Flows Should We Be Talking About?

- Inputs from other researchers are essential to the process of advancing biomedical science
  - Published findings, some of which are patented
  - Unpublished data, knowledge and know-how
  - Materials
- Which of these inputs are historically "public"?
  - Published findings
    - And perhaps the rub is that published findings are now more likely to be patented
- Other inputs largely private, though there is a norm of sharing
- But ready access to all of these inputs contribute to subsequent research and the advance of science

# Our questions

- Where do we see restricted access?
- And what drives such restrictions?

- Consider the effect of IP in the broader context of the range of factors that might condition access to knowledge and other key inputs to biomedical research.
  - So, look at full range of inputs
  - And comprehensively assess role of factors—not just IP—affecting the associated flows

# Starting point: A priority-based recognition-reward system

- Academics' quests for priority of discovery and recognition for such are argued to advance dissemination of knowledge, reconciling private and public interests
- However, reputation due to priority of discovery, as well as many of the inputs upon which such discovery builds, are private, not public goods
- Recognition-based reward system can produce non-cooperative behaviors similar to those attributed to IP, reflecting a range of academic "appropriability strategies"
- But what drives the decision to restrict access, and the choice of what **appropriability strategies** employed?

# Approach

- To understand what might drive restrictions on the flow of research inputs, consider the determinants of the costs and benefits of excluding others from the use of such inputs.

# Private benefits of excluding

- Assuming that exclusion strengthens prospects for priority of discovery (especially follow-on discovery), benefits are:
  - Self-reinforcing academic rewards (cf. Merton, Hagstrom)
    - Reputation, status and prizes
    - Grants, students, etc.
    - Positions and income
  - Commercial rewards
    - Commercial rewards to reputation, as well as to the IP itself, can supplement academic benefits (Zucker and Darby)

# Private costs of excluding

- ***Depends on input in question***
  - IP on a published discovery
    - Hard to detect infringement and costly to enforce
  - Materials and data: Easy to exclude, and sometimes costly to provide access
- Consequences (for holder) of excluding can be costly
  - Granting agency strictures
  - Social opprobrium in a repeat game with mutual dependence
  - Dampening of complementarities associated with reciprocity of knowledge exchange
  - Loss of recognition (Furman & Stern)

# Data

- Post-mail survey: 1,987 biomed researchers
- University, non-profits, government, industry
- Sample frames
  - Professional societies
  - Researchers associated with cell signal proteins: CTLA-4, EGF, NF-kB
- 414 responses from random academic sample, reflecting 40% (adj.) response rate
  - 654 responses in total, including industry and signal protein researchers samples
- Focus on the random "academic" sample, which includes scientists working in universities, non-profit and gov't labs

# Have patents been used to exclude academics from using prior discoveries?

# Rarely

# Do academics seek permission?

- Rarely
- Only 8%, or 32 of 381 academic respondents, even believed they needed knowledge or information covered by patents
- Given burst in research tool patents, why so few?
  - Only 5% check regularly for patents on knowledge or material inputs (little change reported since *Madey v. Duke*)
  - Not related to receiving guidance from institution
- Suggesting lack of concern
  - Per interviews (Walsh et al., 2003), they just want to get their work done

# Impact of "Pure IP"

- Cost of access?
  - When they do seek permission, nearly always (22/23) no cost
- How often does a patent affect academic research?
- How often when the respondent knows there is a relevant patent?

# Impact of "Pure IP"

| Effect | N | % of all respondents (N=381) | % of those knowingly faced w/ patent (N=32) |
|---|---|---|---|
| Delay (> 1 month) | 5 | 1% | 16% |
| Modify | 4 | 1% | 13% |
| Abandon | 0 | 0% | 0% |

# Effects of Patents

- Patents rarely lead to delays or abandoning research
- These findings have been replicated in Japan (Nagaoka, Walsh and Huang, 2007), Australia (Nicol and Nielson) and other US studies (Walsh, et al., 2003; Walsh and Huang, 2007)
- Patents on diagnostics an exception (Cho, Merz)

# Why so little impact?

- Limits on practical excludability
  - Often hard for IP holder to detect others' use
  - Even if detected, enforcement often not cost-effective, even for firms
    - Litigation expensive
    - Payoff low (injunction against others' completing research and reasonable royalties on small-scale use)
    - Loss of added value from infringing academics' exploring the possibilities of the technology is another cost of excluding
    - Lost access to future cooperation, which may be main cost of exclusion
- Thus, cost of excluding others from using IP on research inputs high

# Contrast:
# Materials/Data where excludability is readily achieved

# Background on "Material" Research Inputs

- Examples
  - Cloned gene, organism (mouse), cell line, protein, drug, unpublished information, etc.
- About 75% of our academic respondents requested materials in the prior two years (v. 6% for pure IP)
- Average # of requests (last 2 years)
  - 7 to other academics and 2 to industry

# And why not make it yourself?

- We asked: How important were each of the following in preventing you from producing the input yourself? (5-pt scale)
  - Time/cost 4.34
  - Lack Capabilities 3.06
  - Patent 1.63 (3.2 for drug request)
- Patents (other than if requesting a drug) not a major impediment to making in-house, though time or capabilities may be

**Table 10. Reasons for Not Creating Research Input In-house, Academic Respondents, by Technology Requested and for Signal Proteins; and Industry Respondents.**

| | | Random | Technology Requested | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Sample | UnpInfo | Gene,Cell,etc | Drug | Protein | Data, Soft | Other |
| Time/Cost | Mean | 4.34 | 3.96 | 4.64 | 3.46 | 4.51 | 4.31 | 3.98 |
| Lack Capabilities | Mean | 3.06 | 3.62 | 2.68 | 3.93 | 3.14 | 3.77 | 3.03 |
| Patent | Mean | 1.63 | 1.54 | 1.39 | 3.16 | 1.53 | 1.56 | 1.61 |
| Respondents | N | 295 | 27 | 143 | 26 | 43 | 13 | 43 |

# Excludability

- Use of others' materials requires owner's permission and effort, sometimes considerable.
- Consequently, excluding others from use of your materials not as costly as in case of pure IP
  - Indeed, can often be achieved passively by not responding to a request

# MTA Terms, Negotiations

- Terms (requested)
  - Reach through-38%
  - Royalties-17%
  - Manuscript review-30%
- Except for royalties, academic respondents doing drug discovery tend to be more subject to restrictive terms than those doing basic research
- Industry suppliers tend to impose more restrictive conditions than academic suppliers

# MTA Terms, Negotiations

- About 40% of transfers require MTA
  - More common if request drugs (64%)
- 26% of MTAs (11% of requests) take more than one month to negotiate
- Fees
  - 93% from academic, no charge, < 2% over $1000
  - 85% from industry, no charge, 7% over $1000
- One in nine each year abandon project due to unfulfilled request

# Difficulties in Accessing Tangible Research Inputs

- 19% did not receive last requested research input
- Apparent increase in recent years
  - For academic to academic exchanges in genomics, percent of requests not received:
    - 2003-04 (Walsh, et al): **18%** (+/-3.7%)
    - 1997-99 (Campbell, et al): **10%**
- Delayed research (>1 month): at least 8% of requests (v. 1% for pure IP)
  - Conservative comparison since most refusals are associated with no MTA requests or negotiation
- One in nine scientists each year abandon a project due to unfulfilled request

# Summary: What input flows are restricted?

- Patent-protected published findings: Rarely
  - But, see Murray, et al., showing NIH-DuPont MOUs increased amount and diversity of follow-on research
- Materials and data: 10x
- Thus, it is flow of difficult-to-replicate, privately held property—not "pure" intellectual property—that is much more likely to be restricted.

# Why Do Scientists not Provide/Receive Materials?

Can understand again in term of costs and benefits to the scientist

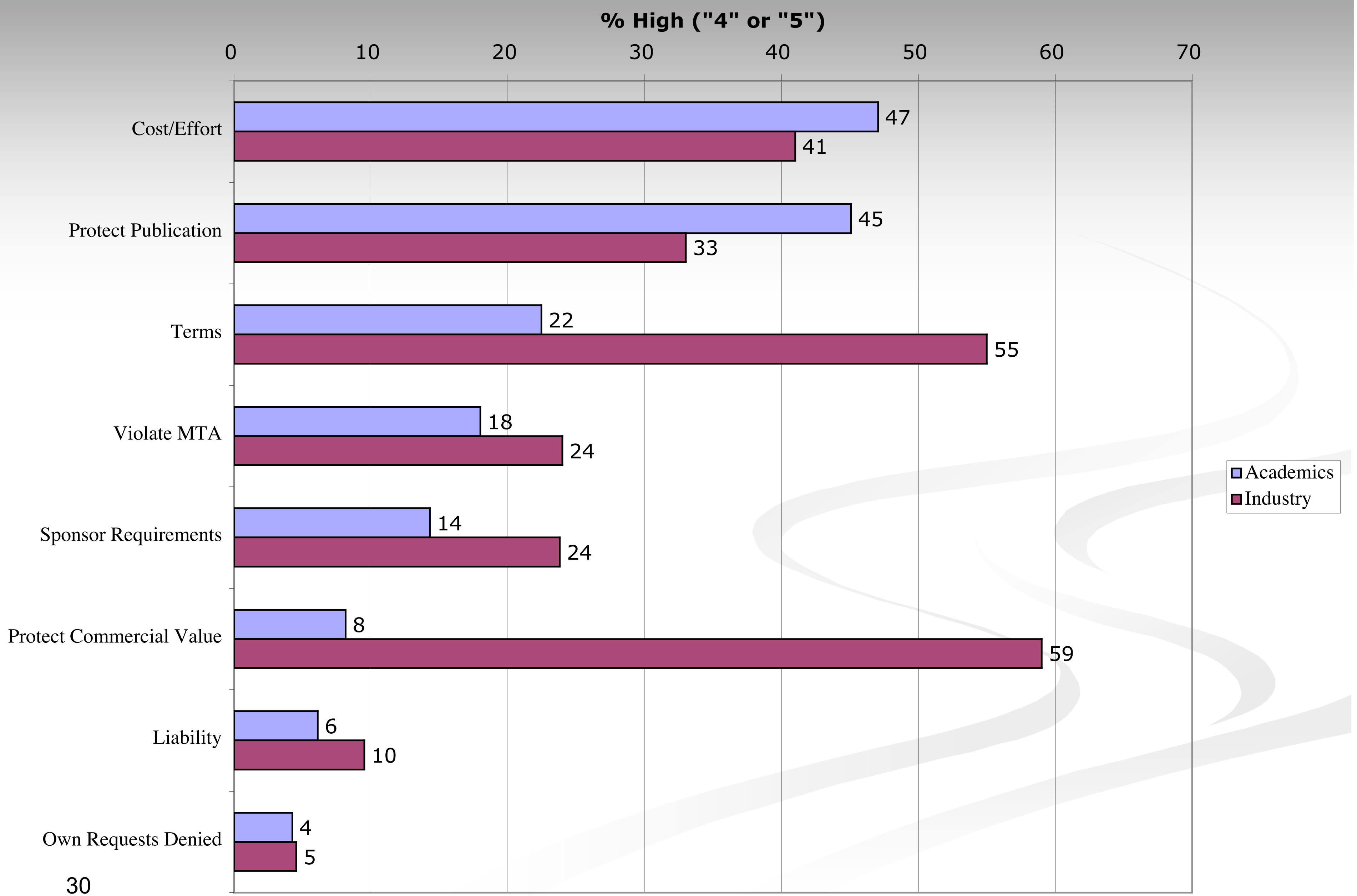
# Costs to Excluding/Providing?

- Provision costs
  - *Response burden**
  - *Prospect of losing priority race**
    - Scientific competition
- Exclusion costs
  - *Practical excludability**
    - High costs for IP, low costs for materials
  - Social and institutional disapproval
    - Example: Non-compliance with NIH guidelines
    - Not yet examined
  - Diminished reciprocal flows and associated complementarities and reduced recognition
    - Also not examined

# Benefits from Excluding Others

- *Greater likelihood of commercial gain (though offset to extent that such activity detracts from academic advance)**
  - IP may play indirect role
- Additional publications (PI, students, other "insiders")
  - Not yet examined
- Grants and research support
  - For example, did the rise in NIH support through the 90's possibly contribute to the observed increase in exclusionary practices in genomics?
    - Not yet examined

**Figure 13. Reasons for not Fulfilling Requests, Academic and Industry Respondents**



# Regressions on supplying and receiving materials

# Negative Binomial Regression for Number of Times Respondent Does Not Fulfill Research Input Requests

| Variable | Model 1 Estimate (s.e.) | Model 2 Estimate (s.e.) |
|---|---|---|
| Business activity | 0.0104* (0.0042) | 0.0101* (0.0042) |
| Number of competing labs | 0.0776* (0.0399) | 0.0735† (0.0406) |
| #Publications | 0.0750* (0.0367) | 0.0754* (0.0366) |
| #Requests Received per $100K Funding | 0.0383* (0.0186) | 0.0341† (0.0195) |
| Total Funding ($100K) | 0.0083 (0.0419) | -0.0017 (0.0460) |
| Industry funding | 0.0058 (0.0051) | 0.0056 (0.0052) |
| Drug discovery | 0.0000 (0.0073) | 0.0002 (0.0073) |
| Male | -0.0077† (0.0044) | -0.0076† (0.0044) |
| #Requests | | 0.0041 (0.0077) |
| Intercept | -2.3391** (0.5112) | -2.2800 (0.5211) |
| Dispersion | 4.0491 (1.0038) | 4.0415 (1.0011) |
| N= | 202 | 202 |
| Chi-square | 148.94 | 150.76 |
| df | 193 | 192 |
| Value/DF | 0.772 | 0.785 |

**Table 4. Logistic Regressions for Receiving Most Recently Requested Material Research Input**

| Variable | Estimate (s.e.) | Estimate (s.e.) |
|---|---|---|
| Drug material requested | -2.2169** (0.6825) | -2.4983** (0.7634) |
| Number of competing labs | -0.0577* (0.0292) | -0.0637* (0.0308) |
| Academic suppliers | 0.00651 (0.00516) | 0.00804 (0.00539) |
| MTA | 0.0124** (0.00420) | -0.00075 (0.00547) |
| Patented | 0.00496 (0.00720) | -0.0116 (0.00951) |
| Patent status unknown | -0.00423 (0.00373) | -0.00864* (0.00430) |
| MTA*Patent | | 0.000380** (0.000133) |
| MTA*Don't know | | 0.000199* (0.000084) |
| Intercept | 1.3605* (0.5934) | 1.5436* (0.6321) |
| N= | 276 | 276 |
| Chi-Square | 33.72 | 44.95 |
| df | 6 | 8 |
| p>Chi-square | <.0001 | <.0001 |

# Why Do Scientists Not Provide/Receive Materials?

- Main predictors
  - **<u>Scientific competition (# competing labs)</u>**
  - Prior business activity
  - Burden (requests/lab dollar)
  - # Publications (eminence or opportunity cost?)
  - Whether material is a drug
- Insignificant
  - Industry funding (modest pos. effect)
  - Drug discovery
  - Patent on material

# Why Do Scientists Not Provide/Receive Materials?

- We also tested the impact of particular terms (reach through, royalty, publication restriction and co-authorship), and found that demanding publication review or royalties reduces the likelihood of completing the transfer

# Case Studies: When infrequent events may have large effects

- Even a rare result can have major social welfare impact if the technology is important enough (e.g., aviation)
- => Collected data from researchers in three fields with high scientific importance and varying levels of patenting and commercial activity
- EGF, NF-kB, CTLA-4
  - Proteins that mediate signals along pathways
  - Lots of research activity
    - Foundational paper 1500 cites for first two, around 900 for CTLA-4
  - Two are prime candidates for adverse outcomes
  - Many patents (760, 90, 60, respectively)
  - Drugs in market or clinical trials

# Case Study Results

- Pure IP: Adverse effects rare, though slightly more common than base rate
  - More likely to know about patents
  - 3% had abandoned a project
- Access to materials even more problematic
  - 26-32% did not receive last request (v. 19% for overall)
  - NF-kB and EGF well above norm in terms of projects abandoned or delayed due to not receiving requested inputs (CTLA-4 near norm)
- Thus, even in high risk areas, the impact of pure IP is small, while the impact of withholding tangible property is even greater than the base rate

# Social welfare effects of exclusion?

- We do not know if exclusionary behavior impedes scientific advance
- Though costly for individuals who suffer from exclusion, collective impact unclear

# Social welfare effects of exclusion?

- For example, may stimulate scientific diversity, offsetting diminishing returns from additional researchers working on a problem
- Ability to exclude, and increased prospect of priority, may stimulate research activity to begin with
- Cost [time, curation resources] of compliance may overwhelm benefit
  - This may be especially true in the case of mandatory pre-compliance [depositing “well-characterized” materials as condition of publication] since most materials are low value

# Conclusion: Impact of "pure IP"

- **Pure IP—Little impact on academic research**
- **"Law on the books" isn't the same as "law in action"**
  - Few are aware of patents, no less ask permission
  - Even when notified by institution to pay attention, they don't
- Why so little attention to patents?
  - Habit formed when patents not so common?
  - Community norms and org/career incentives that value getting the science done, without paying much attention to anything that might slow it down?
  - Or, low likelihood of being sued, so no incentive to change behavior

# Conclusions

- **If there is a problem, it's one of access to *tangible*—not *intellectual*—property, and**
- **The constraints on access turn more on cost/effort, scientific competition and commercial activity than on IP per se**
  - But Bayh-Dole and IP-related legislation that fosters commercial activity among academics plays role
  - But need to weight benefits of such legislation against costs
- Consider the full range of inputs, and the range of factors affecting the costs and benefits of associated flows
  - Niu-opportunity costs of compliance, costs of sanctions/benefits

# Norms of exchange

- But norms are powerful; indeed, it is surprising that there is as much exchange of materials, data, etc. as there is
  - 80-90% of requests fulfilled (depending on who you ask)
  - Over 90% of academics did not delay or limit publications even once in two years
- These "norms" may simply reflect perception of reciprocal benefits associated with exchange

# Norms of exchange

- Thus, norms of exchange and the quest for priority of discovery, and recognition for such, may advance dissemination (at least via publication)—but only to a point
- And that point changes over time and varies across fields
- Thus, left with question of how to get a commitment of the community to new, more open and more collective, norms—and does the community really want this change in behavior?
- Redefine what counts as proper scientific results
- Remember, we are they

# Open Questions

- What are the economic and social factors that condition the costs and benefits of sharing and exclusion of various inputs.
- And don't lose sight of appropriability incentive effects
  - To the extent that rules regarding exchange, such as those of NIH, are enforced what are the effects on incentives to do research to begin with?
  - If we make sharing requirements too onerous, shift research away from tool production and toward exploiting others' well-documented tools?
- What are impacts of exclusion on the pace of science?

# Thank you

# Appendix

# Publication-related Secrecy

- Publication-related secrecy is only modestly present, with over 90% of scientists publishing fully and promptly
  - However, much more common among some groups of scientists
- Commercial activities, research ties with small firms and industry funding increase scientists' withholding behavior, especially among senior scientists
  - Large firms may be more willing to participate in open science (see also AUTM data)

# Publication-related Secrecy

- Commercial activities also have stronger impact for those doing basic research
  - This may be particular cause for concern
  - Undermining open science
- Scientific competition for priority has weak and mixed effects, sometimes decreasing secrecy and sometimes (as in case of excluding information) increasing it

# Publication-related Secrecy

- Also, institutional context is important.
- Those in more entrepreneurial universities engage in **less** secrecy
- May be responding more to changing incentives than to shifting norms
- Suggests that a better-developed TTO can help reduce negative effects of commercial activity on open science

**Table 7. Likelihood of Receiving All Requested Research Inputs, Academic Respondents, by Research Goal and for Signal Proteins; and Industry Respondents.**

| | | Random | Research Goal | | | Signal Proteins | | | Industry |
|---|---|---|---|---|---|---|---|---|---|
| | | Sample | DrugDisc | BasicRsrch | Other | CTLA4 | EGF | NF-kB | Respondents |
| Academic Source | | | | | | | | | |
| Unpublished Information | % yes | 69 | 63 | 70 | 67 | 40 | 33 | 50 | 50 |
| Gene, Organism, etc | % yes | 63 | 68 | 63 | 53 | 45 | 50 | 50 | 52 |
| Drug | % yes | 54 | 43 | 53 | 100 | 57 | 0 | 20 | 35 |
| Protein | % yes | 62 | 56 | 62 | 83 | 53 | 50 | 52 | 38 |
| Database/Software | % yes | 56 | 33 | 58 | 60 | 44 | 29 | 75 | 37 |
| Industry Source | | | | | | | | | |
| Unpublished Information | % yes | 56 | 63 | 57 | 33 | 17 | 20 | 0 | 57 |
| Gene, Organism, etc | % yes | 54 | 43 | 56 | 50 | 44 | 17 | 33 | 53 |
| Drug | % yes | 44 | 44 | 43 | 50 | 44 | 21 | 27 | 57 |
| Protein | % yes | 53 | 67 | 51 | 50 | 38 | 20 | 29 | 50 |
| Database/Software | % yes | 55 | 60 | 50 | 50 | 0 | 0 | 50 | 65 |
| Respondents | N | 152 | 16 | 124 | 12 | 10 | 18 | 12 | 52 |