July 30, 2018

Dr. Courtney Silverthorn
Deputy Director, Technology Partnerships Office
National Institutes of Standards and Technology
100 Bureau Drive MS 2201
Gaithersburg, MD 20899

Dear Dr. Silverthorn,

Thank you for this opportunity to suggest ways of increasing the return on taxpayer dollars invested in R&D. This letter includes suggestions to all current and future participants in our innovation ecosystem, not only to NIST.

I've been an enthusiastic participant in our innovation ecosystem for nearly 40 years, as an engineer, inventor, investor, license negotiator and technology transfer professional, reasonably royalty expert, coach for entrepreneurs, member of grant review committees, and scholar. I received the Association of University Technology Managers "AUTM" Bayh-Dole award in 2017.

This letter is organized around my views on how i) research funding priorities, ii) technology transfer practices, policies and infrastructure, iii) patent law, and iv) tech transfer metrics can further speed moving technologies from lab to market.

BASIC RESEARCH, APPLIED RESEARCH, AND EXPERIMENTAL DEVELOPMENT

We can't afford not to fund basic research:

Basic Research has been defined as "experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundations of phenomena and observable facts, *without any particular application or use in view*.[1]" [Emphasis added]

Nonetheless, even absent a particular application or use in view at the time the Basic Research was performed, the impact of Basic Research itself is in view. Science & Engineering "S&E" Indicator data on research expenditures by performer and by character of work show that most research done at universities and academic institutions is Basic Research. Figure 2 of the most recent application[2] of an Input-Output model[3] to AUTM member inventions illustrates this S&E data.

Figure 3 from the same report shows that the contribution to U.S. GDP from inventions arising from AUTM member performed research grew faster, about twice as fast, as GDP as a whole from 1996-2015[4]. The data do not track or match specific Basic Research expenditures to specific practical impacts (that data may be in iEdison), but do suggest that institutions that do mostly Basic Research make visible contributions to productivity and prosperity.

AUTM's response to the NIST RFI[5] also highlighted new company formation, new product introduction, and the employment supported by these activities: "It is estimated that well over $1 trillion

of economic impact has benefited the nation, creating with it hundreds of new drugs, thousands of new products and companies, and millions of jobs."

January 1980, my first week of a new job at AT&T Bell Laboratories, I was regaled with stories of famous inventors, including Bill Pfann, the celebrated inventor of zone melting [6],[7] (a process used to produce silicon pure enough to make transistors). Bill Pfann often sat with his feet on his desk, pondering. A colleague of Bill Pfann's boss noticed this, and asked the boss why he continued to employ Mr. Pfann. "I can't afford not to", he replied. "We don't know what he will think of next".

Keep and create incentives for disclosure, data gathering, and long term collaboration.

Provide funding and accolades to researchers who:

Publish negative results.
Confirm findings. Being second chronologically is emphatically not second scientifically.
Propose falsifiable hypotheses.

Recognize observers who publish insightful case reports[8], [9], —and the less immediately insightful ones too. For example, modern immunotherapy owes much to work started more than a century ago by William Coley [10],[11] , later curated by Helen Coley Nauts [12],[13]. Reward those who take the time to: "If they see something, write something." It's not all big data. Sometimes there are key clues from a single or a small number of observations.

At the NIST Symposium on Unleashing American Innovation, https://www.nist.gov/tpo/return-investment-roi-initiative/unleashing-american-innovation-symposium Dr. Austin noted that animal experiments imperfectly predict results in people. Observing and writing about outliers, e.g. unusual responders or non responders in clinical trials, can provide important clues with modest incremental cost.

Fund the acquisition and use of curated data, especially when it uncovers a mechanism. At a population level, it was observed that individuals with CCR5-Δ32 mutation were less susceptible to HIV infection, pointing the way to anti CCR5 treatments[14].

Funding the acquisition and use of curated data applies to technology transfer metrics too, as will be described in the metrics section.

Encourage those who think of ways to design more efficient experiments, such as adaptive clinical trials[15]. Biomarkers are useful both i) at the clinical trials stage for patient recruitment and ii) to select patients likely to benefit once treatments have been approved.

Figure 9 of Thomas[16] shows that drugs with biomarkers have three times the likelihood of approval as those without biomarkers. A 2018 paper[17], from the MIT Department of Computer Science and the Sloan School of Management on clinical trial success rates and the impact of biomarkers found that using known biomarkers, especially in oncology (the author caution against over interpreting outside of oncology due to small sample size) essentially doubles the likelihood of approval. Interestingly, they report that studies to identify *novel* biomarkers have the usual more modest success rates.[18]

This suggests that finding novel correlations between biomarkers and health or disease is as challenging as finding therapeutics.

Encourage and reward ambitious long term team efforts.

These achievements remind us of what is possible with coordinated, sustained effort. Examples include:

> The LIGO Scientific Collaboration https://www.ligo.org/ the intergenerational, interdisciplinary, international effort which resulted in the detection of gravity waves from merging black holes, and the possibly even more stunning detection of a neutron star merger only a year later. It's OK to work on a hundred year old theory, and to publish papers with hundreds and even thousands of authors in alphabetical order.
>
> The Encyclopedia of DNA Elements "ENCODE" Project https://www.encodeproject.org/ [19], which began the amazing process of describing the regulatory role played by the 98% of human DNA which, because it did not code for known proteins, had initially been called "junk".[20]

The next successful ambitious project might be a large scale energy storage solution which expands our use of renewable energy and reduces production costs for energy intensive manufacturing.

With respect to applied research and experimental development, start with the end in mind.

If you are a customer of research, tell the performer what you need, as precisely and comprehensively as you can. This will increase the efficiency of technology transfer and thus return on investment of R&D. Too many academic research scientists guess what, exactly, industry wants, and they would prefer not to do so. Sample specifications which can be helpful to a research scientist:

> What properties must the material or machine have? What must it not have?
> What experiments or tests are required to show feasibility?
> For materials and hardware: Reliability tests? Which ones? Performance alone, or performance and manufacturability. Define "manufacturability".
> For biology: Would a demonstration of efficacy suffice, or must the mechanism be fully understood?

Help identify high value problems and challenge researchers to find high value solutions to them.

Reducing carbon emission during aluminum production, apparently now well underway, it is an example of a high value problem which industry may be uniquely positioned to identify[21].

What problems would insurance companies like to see solved? Savings streams are in may respects equivalent to earnings streams. Formally championing efficiency may unleash more and different creativity.

Other possibilities could include:
The aforementioned biomarkers, which could increase the speed, and thus reduce the cost with which new therapeutics are tested and approved.

Large scale energy storage, which per Vaclav Smil, is essential for wider adoption of renewable energy, and could potentially lower the bill for energy used in industrial processes.[22]
Reduce energy use during filtration, -moving from thermal to mechanical processes.[23]
Reduce water use in textile dying. [24]
Reduce recurrence of tumors after surgery [25], [26], [27]
Reduce side effects of medical treatments.[28]
Use combinatorial screening techniques to find combination therapies to treat hard to treat microbial infections, often with already approved pharmaceuticals[29]

Communication: Visual, compelling, consistent, accurate.
Fund and celebrate data visualization. Kudos to

> Edward Tufte https://www.edwardtufte.com/tufte/ a pioneer in the field of the visual display of quantitative information, and inspiration to scientific illustrators and animators.
>
> The Stimulating Extreme Spacetime project https://www.black-holes.org/ , whose software and animations helped us imagine the pair of black holes that collided more than a billion years ago. The code is also being used to make testable predictions.
>
> Carnegie Mellon University's CREATE Lab http://www.cmucreatelab.org/ and Earth Time https://earthtime.org/explore#theme=big_picture_on_nature&story=default , among others.

Might there be more use of adaptive trials if there were an animation illustrating adaptive randomization to patients and their caregivers?

Can animations help explain the notion of risk?

Resist metaphor. Deoxyribonucleic acid is a molecule and not "the language of life". Elevating deoxyribonucleic acid to "the language of life" contributed to unclear patent law, applied unpredictably to our detriment, as will be elaborated upon later in this letter.

Be consistent with language and definitions, especially in highly visible areas. Pedantic and boring is better than misunderstood. As needed, discuss how definitions have changed with time. The definition of "gene" has moved, and continues to move fluidly between the concept of i) "a unit of inheritance", -and thus potentially an "abstract idea" ineligible for patent protection and ii) a molecule and ii) many molecules.[30]

LICENSING AND TECHNOLOGY TRANSFER PRACTICES:

External processes:
Websites with information about process are helpful. Sharing "for external distribution" versions of template agreements are one way to communicate steps in the contract negotiation process.
Share assumptions and perceptions of value and risk, and approaches to capture the former and manage the later.
Explain what an organization can and cannot do.

Identify the negotiators and explain the signatory process.
Discuss and decide what will happen if the collaboration or project does not go as anticipated.

Internal processes:
Empower federal laboratories to assert copyright.
Annotated template agreements for internal use will speed the process. Customized agreements within standard and transparent practices is the goal.
Work with IP counsel to create and maintain commercially meaningful IP protection. This can take the form of asking patent counsel to comment on ease and cost of prosecution, and invite counsel to suggest data or information, which, if present in the patent filing, could reduce prosecution complexity and cost, and potentially enhance the scope of reasonably claimable and enforceable subject matter.
Fund internal office IT systems.

Personnel exchanges:
Encourage personnel from the non profit sector to attend conferences industrial personnel attend, and vice version.

Accelerator funds/ proof of concept grants:
Are effective[31], [32]. Consider expanding funding available for this kind of grant and involve the private sector in the grant review process. Continue involving the private sector as the work progresses.

PATENT LAW:
Patents create incentives both for disclosure and for investment.

Patents both disclose inventions and protect investments, simultaneously fulfilling the academic directive to share information and lowering the risk of for-profit partners to invest in early technologies. Patents can and do start conversations between the for-profit and nonprofit sectors, or between companies. Unlike trade secrets, they expire, thereby inherently incentivizing development of the next new thing. The opposite of patents is trade secrets, not open innovation.

With respect the need to document the importance of expiring exclusivity to new company formation and new product development:

Start-ups need exclusivity to start. AUTM data, collected between 1998- 2006 (the only years the data were collected in this form, both by exclusivity and by type of company), show that more than ninety percent (90%) of the licenses to start-ups were exclusive[33]. Figure 5 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2726797/figure/F5/ of Pressman 2006[34], shows that for start-ups from various AUTM members that licensed patents with DNA sequences in the claims, only one of the 43 licenses was nonexclusive , -the rest were exclusive, all fields of use (29/43), or exclusive by field of use (13/43).

Exclusivity and patents encourage new product development: It is not possible yet to investigate an alternative universe where, because there are more or fewer or different patents than there are today, there are more, or fewer, or different kinds of products. However, it is possible to study product

development outcomes under patent licensing frameworks with more or less exclusivity. Bayh-Dole gives licensors more discretion regarding exclusivity in patent licenses than Stevenson-Wydler, so a comparison of the outcomes of licensing practices under Bayh-Dole and under Stevenson-Wydler may shed light on the question of whether more exclusivity leads to more or faster product commercialization and availability.

Figure 3 of the 2012 paper "DNA Patent Licensing Under Two Policy Frameworks"[35] suggests that a greater percentage of patents (with DNA sequences in the claims) are licensed under Bayh-Dole than under Stevenson-Wydler. Figure 6A suggests that products associated with these patents get to market faster under Bayh-Dole than under Stevenson-Wydler. Figure 4 shows that nonexclusivity does not guarantee availability of product.

The paper as a whole, simply by looking at timing of license execution relative to product introduction, shows that exclusive licenses are more consistent with incentive creation than nonexclusive ones. Exclusive licenses, or more accurately, licenses with some exclusivity in them (licenses can be and often are exclusive by field of use) occur for the most part before the products are introduced, and the licensees seem to keep them longer, as would be expected with the enhanced diligence provisions found in licenses with exclusivity. (Diligence provisions are contractual requirements to develop the technology. If there is insufficient measurable progress, the license can be terminated or made nonexclusive. There provisions are typically found in licenses with exclusivity and absent in licenses without exclusivity.) In contrast, nonexclusive licenses tend to be "just-in-time" or "just-in-case" licenses, executed close to or after product introduction, and simply not kept as long.

With respect to biological materials, those that are patented are, per the full 2005 Walsh Cho Cohen[36] study, are transferred *more* easily than those that are not.

> "In contrast to the effects of access to intellectual property, access to tangible property in the form of material transfers is more likely to impede research." Id page 2.

A recent Master's Thesis[37] from the Utrecht University revisits in detail the question of patents and availability of diagnostic products. There are observations both about the lack of bad things associated with patents, as had been proposed by Heller and Eisenberg[38], and the good things which do happen, such as product development and competition.

> "The research [about the effects of patenting on the development of diagnostic products] showed that patenting does not affect the product development in a significantly different way than other types of patenting. This rejects the hypothesis advanced by Heller and Eisenberg (1998) that gene patenting would hamper the downstream product development. This is in line with the findings of Walsh et al. (2003) that suggested that gene patents do not grant an effective monopoly over products or processes and that working solutions around the IP remain within the reach of competitors.
>
> The presence of patents in a market niche promotes the number of incremental innovations in that market and decreases the strength of the monopoly. These results are in line with literature as it suggested that the number of IP rights present in a market niche supports product development and competition (Cohen & Merrill, 2003; Pressman, 2012; The Lewin Group 2005). At the same time the presence of patents strengthens the barriers to entry. In line with literature this confirms that patents support the production of technological products,

> promote competition and at the same time raises the barriers to entry for competitors (Hellmann, 2007; Kitch, 1977; Leten et al., 2010)." Id pp 41-42

Given all this evidence, it is past time to stop talking about a need to a priori remove patent eligible subject matter lest it improperly "preempt" future innovation.

With respect to the urgent need to restore broad patent eligibility:

I thank Judge Plager for his trenchant and articulate critique of the incoherent stage of patent eligibility law especially regarding abstract ideas in his concurring-in-part and dissenting-in-part brief[39] filed in the Interval Licensing LLC case.

> "'Abstract ideas,' like the term 'obscenity,' may provide a cultural consensus in a given instance regarding whether a past event qualifies, but it fails to provide the kind of specificity and clarity that makes it useful for future prediction of outcome.'"

Judge Plager's practical suggestion that the court defer addressing 101 matters until all 102, 103 or 112 issues are resolved, is appealing: See page 15 of Judge Plager's brief:

> "In the interim, a district court in an appropriate case might choose to exercise control over its docket by instructing a defendant who raises an 'abstract ideas' § 101 defense that the court will defer addressing that defense until first having the issues in §§ 102, 103, and 112 addressed. This need not be viewed as offending existing law since the 'abstract ideas' test would remain in the case, as would the *Alice* process; only the timing would change."

As Judge Plager pointed out, the "tests" for "abstraction" are circular, and essentially a test for obviousness in the eyes of the beholder.

AUTM's suggestion, -that the burden of showing the claimed invention is one of the judicial exceptions should be on patent examiner or court is appealing as well, particularly with respect to purported "natural laws" or "natural phenomenon". As described in the Bilskiblog: Bad Science Makes Bad Patent Law—No Science Makes It Worse, parts I[40] and II[41], natural laws and phenomenon are characterized as such because they make predictions which have not yet been falsified (natural laws) or are widely observed to exist absent human intervention (natural phenomenon).

Scientists, not attorneys are qualified to characterize laws of nature or natural phenomenon as such. If it The analysis framework provided by 102, 103, of 112 is robust, and broad patent eligibility should be restored.

The current state of patent law generally, not only the 101 confusion, but the current state of IPR's and the "not-so-amazing-grace-period" reflects an unsubstantiated and unfavorable attitude toward patents. Fuzzy language, interpreted arbitrarily, and invisible monopolies in the form of never expiring trade secrets create uncertainty and friction. Well defined expiring monopolies motivate inventors, attract investment to the next generation of companies and products, and encourage both collaboration and design arounds, i.e. competition.

METRICS: NO COUNTABILITY, NO ACCOUNTABILITY

This section is primarily about the nonprofit technology transfer community. Note that Chapter 8 of the 2018 S&E Indicators has Invention, Knowledge, and Innovation data[42], which currently include selected AUTM and federal laboratory data, in appendix tables 8-26 and 8-27, respectively.

Why: Without measurement, there is no ability to track progress toward goals.

What: Pick a few good things to count, define them well, with input and buy in from data providers and users, and count them over decades. The AUTM Survey is an excellent place to start. AUTM members created it first to help understand and manage their own offices, and in due course, to understand the effect of their activities outside of their offices. It is understood that federal laboratories perform technology transfer under a different policy framework than universities do, that they have different mission statements and funding patterns.[43] There may be reasons for federal laboratories to count things that universities do not count and vice versa. This is no reason not to pick a few good things to count, define them well, with input and buy in from data providers and users, and count them over decades.

Pick at least some of your data elements mindful of standard economic metrics, such as GDP and jobs. New is good. Standard and supported by an established consensus is vital.

It is important to count over long time periods for several reasons. Impacts of research can and do occur decades after it was performed[44], [45]. Tech transfer is affected by macroeconomic conditions unrelated to tech transfer. There is large variability in technology transfer outcomes, even when there are large numbers of projects. Here is the abstract in full of the classic 2000 Scherer Harhoff paper[46] "Technology policy for a world of skew-distributed outcomes". (Emphasis added.)

> This paper draws implications for technology policy from evidence on the size distribution of returns from eight sets of data on inventions and innovations attributable to private sector firms and universities. The distributions are all highly skew; the top 10% of sample members captured from 48 to 93 percent of total sample returns. It follows that programs seeking to advance technology should not be judged negatively if they lead to numerous economic failures; rather, emphasis should be placed on the relatively few big successes. To achieve noteworthy success with appreciable confidence, a sizeable array of projects must often be supported. *The outcome distributions are sufficiently skewed that, even with large numbers of projects, it is not possible to diversify away substantial residual variability through portfolio strategies.*

The twenty years of AUTM data noted earlier in this letter are lumpy. There were high earned royalty payments in 2007-2009. When data fluctuate, trends become credible only when there are enough data to make the outliers look like outliers, and the trend is seen without them.

How many is "a few good things go count"? Probably a few dozen. There are operational metrics, including FTE's in tech transfer offices, and patent budgets. There are activity metrics, such as invention disclosures received, patents filed, and contracts signed. There are outcome measures, such as earned royalty received, start-ups formed and or funded, and new technologies introduced.

Some of these inherently demonstrate interest on the part of industry, such as license contracts, and payments made under these contracts. The types of payments can show the types of activities at the licensees. An earned royalty is evidence that the corporate partner is making a product.

Some nuance on the type of contract is useful, such as exclusivity. See the above section on patent law. It is helpful to be able to quantitatively and objective support the need for proprietary rights in the innovation ecosystem.

Nuance on the type of intellectual property would also be useful as would the information on the size of the licensees (ideally, both when the license is signed and when the earned royalties are received), and the technical field of the technology licensed. Counting the number of new products and new companies is very important, as would be detail on the products and companies.

Ideally, it would also be helpful to know the locations of manufacture and sale of the licensed products.

Other valuable information: Pajek diagrams, or connectivity maps, can play an important role in illustrating connections between funders, performers, and users of research. They are used in citation mapping of peer reviewed publications and patents. They can also be used to show commercial connections. See Powell[47].

Include product narratives and start collecting simple information that can be used to classify them. It is worth doing this retrospectively as well. What was the type of intellectual property with which the product is associated? Patents, biological material, copyrighted software, other? Which entities funded the research, which entities performed it? Add the dates, -when was the intellectual property disclosed, when licensed, when was a product first sold? What is the technical field of the product? NAICS codes can be used to classify the products. These extra classifiers will dramatically change the value of the product narratives.

Timelines are a key and somewhat neglected metric. Databases often have information on date of invention disclosure, patent filing, license execution, first earned royalty, and when/if the license was terminated. See figures 4, 6A and 6B of "DNA Patent Licensing Under Two Policy Frameworks" for an example of the usefulness of such data. Timelines are probably the low hanging fruit of useful and infrequently used metrics. Timelines should also be derivable from iEdison.

How: Data acquisition.
Ultimately, for scale, consistency, quality control, and usefulness, involve the S&E Indicator team.

Ultimately, for ease of response, the data should come as much as possible from existing office databases, or even from existing databases, such as iEdison. If we can invent quantum computers, we can facilitate acquisition of technology transfer data.

Can commercial providers of technology transfer databases, such as Wellspring be brought into the process?

Meanwhile: A web interface (such as the one currently used by AUTM) for data entry provides an opportunity for simple error checking and quality control at the time of data entry.

Good survey and data management practices:
Post the survey instrument so definitions are easily findable.
Post it for every year it is used. Definitions do change, fields are added or subtracted, and data availability by year should be readily available and findable.
Post or make easily findable, the response rate. Ideally, post the response rate *for each question*.
Make it possible to look easily at recurrent respondents, ideally on a per question basis.
Make the interinstitutional relational database available to scholars (under CDA if needed).
Have a human contact available to answer questions and to elicit or clarify responses.
Aggregate as needed to preserve confidentiality.
Present the data so respondents continue to find providing it useful to them as well as to other users.

Use a web interface to collect the product narratives, and use the web format to request the classifiers described above (type of intellectual property, dates, etc…) to build a searchable database of products.

How: Data presentation and display
Keep reporting what we report.

Add more information on response rates, distributions of values (skew), and predictive classifiers, such as figures 11, 12 and 13 in the FY2001 AUTM . These histograms show the probability of generating a certain level of license income goes up with the age of the program, the amount of research expenditures at the institution as a whole, and the number of active licenses. These figures illustrate that technology transfer takes time, and that while an "installed base" of license agreements and high research expenditures increases the likelihood of bringing in a certain amount of revenue, there is no guarantee. This kind of analysis can be done for any pair of properties, FTE's and start-ups for example.

Work with CMU's CREATE Lab and others at the forefront of data and network visualization.

Sincerely,

Lori Pressman

[1] There is a standard reference for characterizing types of R&D called the Frascati Manual, available here: http://www.oecd.org/sti/frascati-manual-2015-9789264239012-en.htm Here are the definitions of types of research:
Basic research is experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundations of phenomena and observable facts, without any particular application or use in view.
Applied research is original investigation undertaken in order to acquire new knowledge. It is, however, directed primarily towards a specific, practical aim or objective.
Experimental development is systematic work, drawing on knowledge gained from research and practical experience and producing additional knowledge, which is directed to producing new products or processes or to improving existing products or processes.

[2] Pressman, Lori, Planting, Mark, Yuskavage, Robert, Okubo, Sumiye, Moylan, Carol and Bond, Jennifer "The Economic Contribution of University/Nonprofit Inventions in the United States 1996-2015", June 2017, Report for BIO and AUTMhttps://www.autm.net/AUTMMain/media/Advocacy/Documents/June-2017-Update-of-I-O-Economic-Impact-Model.pdf

[3] Roessner, David, Bond, Jennifer, Okubo, Sumiye, Planting, Mark. 2013. "The Economic Impact of Licensed Commercialized Inventions Originating in University Research", *Research Policy* 42(1): (February) 23-34

[4] The I-O modeled AUTM member contribution to U.S. GDP is very small. In 1996, it would be roughly a tenth of one percent ($10.8B out of $10.6T), and in 2015 a little more than two tenths of a percent ($36.7B out of $16.4T)

[5] https://www.autm.net/AUTMMain/media/Advocacy/Documents/AUTM-Comments-on-Federal-Technology-Transfer-Authorities-and-Processes-Docket-180220199%E2%80%90819%E2%80%9001.pdf

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[15] https://www.berryconsultants.com/library/ and https://www.ispytrials.org/ispypeople/leadership

[16] Thomas, David W., Burns, Justin, Audette, John , Carol, Adam, Dow-Hygelund, Corey, Hay, Michael. 2016. "Clinical Development Success Rates 2006-2015", Prepared by BIO, Biomedtracker and Amplion, 2016 Figure 9 is on page 18.

[17] Wong CH, Siah KW, Lo AW. 2018 "Estimation of clinical trial success rates and related parameters" *Biostatistics* (2018) **00**, 00, *pp.* 1–14

[18] Table 3 shows only trials that use biomarkers to stratify patients. As can be seen, there is substantial variation in the use of biomarkers across therapeutic areas. Biomarkers are seldom used outside of oncology. Trials using biomarkers exhibit almost twice the overall POS (POS1,APP) compared to trials without biomarkers (10.3% vs. 5.5%). While the use of biomarkers in the stratification of patients improves the POS in all phases, it is most significant in Phases 1 and 2. (We caution against over-interpreting the results for therapeutic areas outside oncology due to their small sample size.) These findings are similar in spirit to the analysis by Thomas *and others* (2016), which also found substantial improvement in the overall POS when biomarkers were used.
However, when we expanded the definition of a biomarker trial to include trials with the objective of evaluating or identifying the use of any novel biomarker as an indicator of therapeutic efficacy or toxicity, in addition to the selection of patients, we obtained significantly different results (see Table S3 in Section A6 of the supplementary material available at *Biostatistics* online). Instead of finding a huge increase in the overall POS, we find no significant difference. It may be that trials that attempt to evaluate the effectiveness of biomarkers are more likely to fail, leading to a lower overall POS compared to trials that only use biomarkers in patient stratification. Comparison of the two tables shows that new biomarkers are being evaluated in all therapeutic areas.

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[33] Table 1. Fraction of licenses to start-ups that are exclusive. Data are from the AUTM STATT database These are the only years that the information is available in this form. Subsequent years have data by exclusivity, but not further categorized by company type (large entity, small entity or start-ups) and data by company type, but not further categorized by exclusivity.

Year	Start Up Exclusive	Startup Nonexclusive	% Startup Exclusive
1998	291	28	91%
1999	346	38	90%
2000	477	47	91%
2001	467	52	90%
2002	491	51	91%
2003	491	32	94%
2004	558	60	90%
2005	514	53	91%
2006	638	60	91%

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