## 1

### Framing

#### Synthetic a posteriori moral naturalism is the basis of ethics:

#### A] The normative supervenes on the natural – natural facts like whether brains develop to permit rationality or subjectivity determine whether non naturalist moral facts can be premised on things like capacity for reason

**Lutz and Lenman 18.** Lutz, Matthew and Lenman, James, "Moral Naturalism", The Stanford Encyclopedia of Philosophy (Fall 2018 Edition), Edward N. Zalta (ed.), URL = <https://plato.stanford.edu/archives/fall2018/entries/naturalism-moral/>. //Massa

The first argument against normative non-naturalism concerns normative supervenience. **The normative supervenes on the natural; in all** metaphysically **possible worlds in which the natural facts are the same as** they are in **the actual world, the moral facts are the same** as well. **This** claim **has been called the “least controversial thesis in metaethics”** (Rosen forthcoming); **it is very widely accepted.** But it is also a striking fact that stands in need of some explanation. **For naturalists**, such an explanation is easy to provide: **the moral facts just are natural facts, so when we consider worlds that are naturally the same** as the actual world, **we will ipso facto be considering worlds that are morally the same** as the actual world. But for the non-naturalist, no such explanation seems available. In fact, **it seems** to be in principle **impossible for a non-naturalist to explain how the moral supervenes on the natural.** And if the non-naturalist can offer no explanation of this phenomenon that demands explanation, this is a heavy mark against non-naturalism (McPherson 2012).

#### That outweighs – controversy prevents acting on moral laws, but lack of philosophical controversy on the correlation between moral and natural facts indicates naturalism guides action.

#### B] The problem of disagreement – resolving a priori conflicts requires indicting the epistemological basis of one’s judgement with a reliable process for deriving moral truths which is impossible given widespread moral disagreement about non verifiable a priori truth – grounding ethics with verifiable natural facts solve

**Copp 7**, D. Why Naturalism? Morality in a Natural World, 33–54. doi:10.1017/cbo9780511497940.003 //Massa

**Suppose**, for example, **that I witness a bullfight and observe that many** thousands of **people who seem to be good-hearted** and fair-minded **see nothing wrong in the treatment of the bull that takes place.** As a result, I might **begin to doubt that bullfighting is wrong, despite the "harsh treatment" of bulls that is involved** in bullfighting. **But whether or not I** begin to **have doubts, if I cannot justify** on independent grounds the claim **that I am better placed epistemically to judge bullfighting than the people who attend** bullfights, **then the fact that so many people disagree** with me about the wrongness of bullfighting would appear to **constitute evidence against my belief** that bullfighting is wrong, undermining or weakening my war rant for the belief. **If this is correct, then the proposition that bullfighting is wrong is not strongly a priori** - unless the undermining effect of the disagreement on the credibility of the proposition is due to psychological weaknesses or computational limitations or to the lack of a full conceptual repertoire such that the disagreement would not undermine the credibility of the proposition to an ideal thinker.

#### Next, phenomenal introspection can bridge the gap from experiential natural facts to moral truths and necessitates hedonism. When I observe a lemon’s yellowness shifting my visual fields from darker to lighter shades, I can introspect on that experience and identify brightness as an intrinsic property of seeing a lemon. Similarly, when I feel pleasure, I can introspect on the shift in hedonic tones and identify that goodness is an intrinsic property of the pleasure that was increased.

#### This connection between pain and pleasure and phenomenal conceptions of intrinsic value and disvalue is irrefutable – everything else regresses – robust neuroscience proves.

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**Pleasure** is not only one of the three primary reward functions but it also **defines reward.** As homeostasis explains the functions of only a limited number of rewards, the principal reason why particular stimuli, objects, events, situations, and activities are rewarding may be due to pleasure. This applies first of all to sex and to the primary homeostatic rewards of food and liquid and extends to money, taste, beauty, social encounters and nonmaterial, internally set, and intrinsic rewards. Pleasure, as the primary effect of rewards, drives the prime reward functions of learning, approach behavior, and decision making and provides the **basis for hedonic theories** of reward function. We are attracted by most rewards and exert intense efforts to obtain them, just because they are enjoyable [10]. Pleasure is a passive reaction that derives from the experience or prediction of reward and may lead to a long-lasting state of happiness. The word happiness is difficult to define. In fact, just obtaining physical pleasure may not be enough. One key to happiness involves a network of good friends. However, it is not obvious how the higher forms of satisfaction and pleasure are related to an ice cream cone, or to your team winning a sporting event. Recent multidisciplinary research, using both humans and detailed invasive brain analysis of animals has discovered some critical ways that the brain processes pleasure [14]. Pleasure as a hallmark of reward is sufficient for defining a reward, but it may not be necessary. A reward may generate positive learning and approach behavior simply because it contains substances that are essential for body function. When we are hungry, we may eat bad and unpleasant meals. A monkey who receives hundreds of small drops of water every morning in the laboratory is unlikely to feel a rush of pleasure every time it gets the 0.1 ml. Nevertheless, with these precautions in mind, we may define any stimulus, object, event, activity, or situation that has the potential to produce pleasure as a reward. In the context of reward deficiency or for disorders of addiction, homeostasis pursues pharmacological treatments: drugs to treat drug addiction, obesity, and other compulsive behaviors. The theory of allostasis suggests broader approaches - such as re-expanding the range of possible pleasures and providing opportunities to expend effort in their pursuit. [15]. It is noteworthy, the first animal studies eliciting approach behavior by electrical brain stimulation interpreted their findings as a discovery of the brain’s pleasure centers [16] which were later partly associated with midbrain dopamine neurons [17–19] despite the notorious difficulties of identifying emotions in animals. Evolutionary theories of pleasure: The love connection BO:D Charles Darwin and other biological scientists that have examined the biological evolution and its basic principles found various mechanisms that steer behavior and biological development. Besides their theory on natural selection, it was particularly the sexual selection process that gained significance in the latter context over the last century, especially when it comes to the question of what makes us “what we are,” i.e., human. However, the capacity to sexually select and evolve is not at all a human accomplishment alone or a sign of our uniqueness; yet, we humans, as it seems, are ingenious in fooling ourselves and others–when we are in love or desperately search for it. It is well established that modern biological theory conjectures that **organisms are** the **result of evolutionary competition.** In fact, Richard Dawkins stresses gene survival and propagation as the basic mechanism of life [20]. Only genes that lead to the fittest phenotype will make it. It is noteworthy that the phenotype is selected based on behavior that maximizes gene propagation. To do so, the phenotype must survive and generate offspring, and be better at it than its competitors. Thus, the ultimate, distal function of rewards is to increase evolutionary fitness by ensuring the survival of the organism and reproduction. It is agreed that learning, approach, economic decisions, and positive emotions are the proximal functions through which phenotypes obtain other necessary nutrients for survival, mating, and care for offspring. Behavioral reward functions have evolved to help individuals to survive and propagate their genes. Apparently, people need to live well and long enough to reproduce. Most would agree that homo-sapiens do so by ingesting the substances that make their bodies function properly. For this reason, foods and drinks are rewards. Additional rewards, including those used for economic exchanges, ensure sufficient palatable food and drink supply. Mating and gene propagation is supported by powerful sexual attraction. Additional properties, like body form, augment the chance to mate and nourish and defend offspring and are therefore also rewards. Care for offspring until they can reproduce themselves helps gene propagation and is rewarding; otherwise, many believe mating is useless. According to David E Comings, as any small edge will ultimately result in evolutionary advantage [21], additional reward mechanisms like novelty seeking and exploration widen the spectrum of available rewards and thus enhance the chance for survival, reproduction, and ultimate gene propagation. These functions may help us to obtain the benefits of distant rewards that are determined by our own interests and not immediately available in the environment. Thus the distal reward function in gene propagation and evolutionary fitness defines the proximal reward functions that we see in everyday behavior. That is why foods, drinks, mates, and offspring are rewarding. There have been theories linking pleasure as a required component of health benefits salutogenesis, (salugenesis). In essence, under these terms, pleasure is described as a state or feeling of happiness and satisfaction resulting from an experience that one enjoys. Regarding pleasure, it is a double-edged sword, on the one hand, it promotes positive feelings (like mindfulness) and even better cognition, possibly through the release of dopamine [22]. But on the other hand, pleasure simultaneously encourages addiction and other negative behaviors, i.e., motivational toxicity. It is a complex neurobiological phenomenon, relying on reward circuitry or limbic activity. It is important to realize that through the “Brain Reward Cascade” (BRC) endorphin and endogenous morphinergic mechanisms may play a role [23]. While natural rewards are essential for survival and appetitive motivation leading to beneficial biological behaviors like eating, sex, and reproduction, crucial social interactions seem to further facilitate the positive effects exerted by pleasurable experiences. Indeed, experimentation with addictive drugs is capable of directly acting on reward pathways and causing deterioration of these systems promoting hypodopaminergia [24]. Most would agree that pleasurable activities can stimulate personal growth and may help to induce healthy behavioral changes, including stress management [25]. The work of Esch and Stefano [26] concerning the link between compassion and love implicate the brain reward system, and pleasure induction suggests that social contact in general, i.e., love, attachment, and compassion, can be highly effective in stress reduction, survival, and overall health. Understanding the role of neurotransmission and pleasurable states both positive and negative have been adequately studied over many decades [26–37], but comparative anatomical and neurobiological function between animals and homo sapiens appear to be required and seem to be in an infancy stage. Finding happiness is different between apes and humans As stated earlier in this expert opinion one key to happiness involves a network of good friends [38]. However, it is not entirely clear exactly how the higher forms of satisfaction and pleasure are related to a sugar rush, winning a sports event or even sky diving, all of which augment dopamine release at the reward brain site. Recent multidisciplinary research, using both humans and detailed invasive brain analysis of animals has discovered some critical ways that the brain processes pleasure. Remarkably, there are pathways for ordinary liking and pleasure, which are limited in scope as described above in this commentary. However, there are **many brain regions**, often termed hot and cold spots, that significantly **modulate** (increase or decrease) our **pleasure or** even produce **the opposite** of pleasure— that is disgust and fear [39]. One specific region of the nucleus accumbens is organized like a computer keyboard, with particular stimulus triggers in rows— producing an increase and decrease of pleasure and disgust. Moreover, the cortex has unique roles in the cognitive evaluation of our feelings of pleasure [40]. Importantly, the interplay of these multiple triggers and the higher brain centers in the prefrontal cortex are very intricate and are just being uncovered. Desire and reward centers It is surprising that many different sources of pleasure activate the same circuits between the mesocorticolimbic regions (Figure 1). Reward and desire are two aspects pleasure induction and have a very widespread, large circuit. Some part of this circuit distinguishes between desire and dread. The so-called pleasure circuitry called “REWARD” involves a well-known dopamine pathway in the mesolimbic system that can influence both pleasure and motivation. In simplest terms, the well-established mesolimbic system is a dopamine circuit for reward. It starts in the ventral tegmental area (VTA) of the midbrain and travels to the nucleus accumbens (Figure 2). It is the cornerstone target to all addictions. The VTA is encompassed with neurons using glutamate, GABA, and dopamine. The nucleus accumbens (NAc) is located within the ventral striatum and is divided into two sub-regions—the motor and limbic regions associated with its core and shell, respectively. The NAc has spiny neurons that receive dopamine from the VTA and glutamate (a dopamine driver) from the hippocampus, amygdala and medial prefrontal cortex. Subsequently, the NAc projects GABA signals to an area termed the ventral pallidum (VP). The region is a relay station in the limbic loop of the basal ganglia, critical for motivation, behavior, emotions and the “Feel Good” response. This defined system of the brain is involved in all addictions –substance, and non –substance related. In 1995, our laboratory coined the term “Reward Deficiency Syndrome” (RDS) to describe genetic and epigenetic induced hypodopaminergia in the “Brain Reward Cascade” that contribute to addiction and compulsive behaviors [3,6,41]. Furthermore, ordinary “liking” of something, or pure pleasure, is represented by small regions mainly in the limbic system (old reptilian part of the brain). These may be part of larger neural circuits. In Latin, hedus is the term for “sweet”; and in Greek, hodone is the term for “pleasure.” Thus, the word Hedonic is now referring to various subcomponents of pleasure: some associated with purely sensory and others with more complex emotions involving morals, aesthetics, and social interactions. The capacity to have pleasure is part of being healthy and may even extend life, especially if linked to optimism as a dopaminergic response [42]. Psychiatric illness often includes symptoms of an abnormal inability to experience pleasure, referred to as anhedonia. A negative feeling state is called dysphoria, which can consist of many emotions such as pain, depression, anxiety, fear, and disgust. Previously many scientists used animal research to uncover the complex mechanisms of pleasure, liking, motivation and even emotions like panic and fear, as discussed above [43]. However, as a significant amount of related research about the specific brain regions of pleasure/reward circuitry has been derived from invasive studies of animals, these cannot be directly compared with subjective states experienced by humans. In an attempt to resolve the controversy regarding the causal contributions of mesolimbic dopamine systems to reward, we have previously evaluated the three-main competing explanatory categories: “liking,” “learning,” and “wanting” [3]. That is, dopamine may mediate (a) liking: the hedonic impact of reward, (b) learning: learned predictions about rewarding effects, or (c) wanting: the pursuit of rewards by attributing incentive salience to reward-related stimuli [44]. We have evaluated these hypotheses, especially as they relate to the RDS, and we find that the incentive salience or “wanting” hypothesis of dopaminergic functioning is supported by a majority of the scientific evidence. Various neuroimaging studies have shown that anticipated behaviors such as sex and gaming, delicious foods and drugs of abuse all affect brain regions associated with reward networks, and may not be unidirectional. Drugs of abuse enhance dopamine signaling which sensitizes mesolimbic brain mechanisms that apparently evolved explicitly to attribute incentive salience to various rewards [45]. Addictive substances are voluntarily self-administered, and they enhance (directly or indirectly) dopaminergic synaptic function in the NAc. This activation of the brain reward networks (producing the ecstatic “high” that users seek). Although these circuits were initially thought to encode a set point of hedonic tone, it is now being considered to be far more complicated in function, also encoding attention, reward expectancy, disconfirmation of reward expectancy, and incentive motivation [46]. The argument about addiction as a disease may be confused with a predisposition to substance and nonsubstance rewards relative to the extreme effect of drugs of abuse on brain neurochemistry. The former sets up an individual to be at high risk through both genetic polymorphisms in reward genes as well as harmful epigenetic insult. Some Psychologists, even with all the data, still infer that addiction is not a disease [47]. Elevated stress levels, together with polymorphisms (genetic variations) of various dopaminergic genes and the genes related to other neurotransmitters (and their genetic variants), and may have an additive effect on vulnerability to various addictions [48]. In this regard, Vanyukov, et al. [48] suggested based on review that whereas the gateway hypothesis does not specify mechanistic connections between “stages,” and does not extend to the risks for addictions the concept of common liability to addictions may be more parsimonious. The latter theory is grounded in genetic theory and supported by data identifying common sources of variation in the risk for specific addictions (e.g., RDS). This commonality has identifiable neurobiological substrate and plausible evolutionary explanations. Over many years the controversy of dopamine involvement in especially “pleasure” has led to confusion concerning separating motivation from actual pleasure (wanting versus liking) [49]. We take the position that animal studies cannot provide real clinical information as described by self-reports in humans. As mentioned earlier and in the abstract, on November 23rd, 2017, evidence for our concerns was discovered [50] In essence, although nonhuman primate brains are similar to our own, the disparity between other primates and those of human cognitive abilities tells us that surface similarity is not the whole story. Sousa et al. [50] small case found various differentially expressed genes, to associate with pleasure related systems. Furthermore, the dopaminergic interneurons located in the human neocortex were absent from the neocortex of nonhuman African apes. Such differences in neuronal transcriptional programs may underlie a variety of neurodevelopmental disorders. In simpler terms, the system controls the production of dopamine, a chemical messenger that plays a significant role in pleasure and rewards. The senior author, Dr. Nenad Sestan from Yale, stated: “Humans have evolved a dopamine system that is different than the one in chimpanzees.” This may explain why the behavior of humans is so unique from that of non-human primates, even though our brains are so surprisingly similar, Sestan said: “It might also shed light on why people are vulnerable to mental disorders such as autism (possibly even addiction).” Remarkably, this research finding emerged from an extensive, multicenter collaboration to compare the brains across several species. These researchers examined 247 specimens of neural tissue from six humans, five chimpanzees, and five macaque monkeys. Moreover, these investigators analyzed which genes were turned on or off in 16 regions of the brain. While the differences among species were subtle, **there was** a **remarkable contrast in** the **neocortices**, specifically in an area of the brain that is much more developed in humans than in chimpanzees. In fact, these researchers found that a gene called tyrosine hydroxylase (TH) for the enzyme, responsible for the production of dopamine, was expressed in the neocortex of humans, but not chimpanzees. As discussed earlier, dopamine is best known for its essential role within the brain’s reward system; the very system that responds to everything from sex, to gambling, to food, and to addictive drugs. However, dopamine also assists in regulating emotional responses, memory, and movement. Notably, abnormal dopamine levels have been linked to disorders including Parkinson’s, schizophrenia and spectrum disorders such as autism and addiction or RDS. Nora Volkow, the director of NIDA, pointed out that one alluring possibility is that the neurotransmitter dopamine plays a substantial role in humans’ ability to pursue various rewards that are perhaps months or even years away in the future. This same idea has been suggested by Dr. Robert Sapolsky, a professor of biology and neurology at Stanford University. Dr. Sapolsky cited evidence that dopamine levels rise dramatically in humans when we anticipate potential rewards that are uncertain and even far off in our futures, such as retirement or even the possible alterlife. This may explain what often motivates people to work for things that have no apparent short-term benefit [51]. In similar work, Volkow and Bale [52] proposed a model in which dopamine can favor NOW processes through phasic signaling in reward circuits or LATER processes through tonic signaling in control circuits. Specifically, they suggest that through its modulation of the orbitofrontal cortex, which processes salience attribution, dopamine also enables shilting from NOW to LATER, while its modulation of the insula, which processes interoceptive information, influences the probability of selecting NOW versus LATER actions based on an individual’s physiological state. This hypothesis further supports the concept that disruptions along these circuits contribute to diverse pathologies, including obesity and addiction or RDS.

#### Finally, the Darwinian dilemma proves the accuracy of introspection and the failure of every non utilitarian ethic. Moral beliefs we hold have shift as we evolve which means either moral facts have changed which contradicts moral realism or evolution has randomly just now led us to moral truth. The latter is statistically impossible since evolution doesn’t track morality – there is no pressure to identify moral truths that have no bearing on survival and reproduction.

#### Hedonism escapes this dilemma through the byproduct hypothesis since natural selection proves the reliability of phenomenal introspection. When we introspect for survival on data from our eyes or ears, such as whether one sees or smells food or a predator, we use the same part of the brain that introspects on hedonic tones and identifies their moral relevance. The ability to correctly identify moral truths is evolutionarily advantageous if and only if that ability is a byproduct of a different trait that enables survival and reproduction.

#### Thus, the standard is consistency with hedonic act utilitarianism. Prefer it:

#### [1] Moral uncertainty means preventing extinction should be our highest priority. **Bostrom** **12** [Nick Bostrom. Faculty of Philosophy & Oxford Martin School University of Oxford. “Existential Risk Prevention as Global Priority.” Global Policy (2012)] <https://www.existential-risk.org/concept.html#:~:text=Existential%20Risk%20Prevention%20as%20Global%20Priority%20ABSTRACT%3A%20Existential,in%20net%20existential%20risk%20have%20enormous%20expected%20value.> These reflections on moral uncertainty suggest an alternative, complementary way of looking at existential risk; they also suggest a new way of thinking about the ideal of sustainability. Let me elaborate.¶ Our present understanding of axiology might well be confused. We may not now know — at least not in concrete detail — what outcomes would count as a big win for humanity; we might not even yet be able to imagine the best ends of our journey. If we are indeed profoundly uncertain about our ultimate aims, then we should recognize that there is a great option value in preserving — and ideally improving — our ability to recognize value and to steer the future accordingly. Ensuring that there will be a future version of humanity with great powers and a propensity to use them wisely is plausibly the best way available to us to increase the probability that the future will contain a lot of value. To do this, we must prevent any existential catastrophe.

#### [2] Actor specificity –

#### A] Governments must aggregate because their policies benefit some and harm others so the only non-arbitrary way to prioritize is by helping the most amount of people

Mack 4 [(Peter, MBBS, FRCS(Ed), FRCS (Glasg), PhD, MBA, MHlthEcon) “Utilitarian Ethics in Healthcare.” International Journal of the Computer, the Internet, and Management Vol. 12, No.3. 2004. Department of Surgery. Singapore General Hospital.] SJDI

Medicine is a costly science, but of greater concern to the health economist is that it is also a limitless art. Every medical advance created new needs that did not exist until the means of meeting them came into existence. Physicians are reputed to have an infinite capacity to do ever more things, and perform ever more expensive interventions for their patients so long as any of their patients’ health needs remain unfulfilled. The traditional stance of the physician is that each patient is an isolated universe. When confronted with a situation in which his duty involves a competition for scarce medications or treatments, he would plead the patient’s cause by all methods, short of deceit. However, when the physician’s decision involves more than just his own patient, or has some commitment to public health, other issues have to be considered. He then has to recognise that the unbridled advocacy of the patient may not square with what the economist perceives to be the most advantageous policy to society as a whole. Medical professionals characteristically deplore scarcities. Many of them are simply not prepared to modify their intransigent principle of unwavering duty to their patients’ individual interest. However, in decisions involving multiple patients, making available more medication, labour or expenses for one patient will mean leaving less for another. The physician is then compelled by his competing loyalties to enter into a decision mode of one versus many, where the underlying constraint is one of finiteness of the commodities. Although the medical treatment may be simple and inexpensive in many instances, there are situations such as in renal dialysis, where prioritisation of treatment poses a moral dilemma because some patients will be denied the treatment and perish. Ethics and economics share areas of overlap. They both deal with how people should behave, what policies the state should pursue and what obligations citizens owe to their governments. The centrality of the human person in both normative economics and normative ethics is pertinent to this discussion. Economics is the study of human action in the marketplace whereas ethics deals with the “rightness” or “wrongness” of human action in general. Both disciplines are rooted in human reason and human nature and the two disciplines intersect at the human person and the analysis of human action. From the economist’s perspective, ethics is identified with the investigation of rationally justifiable bases for resolving conflict among persons with divergent aims and who share a common world. Because of the scarcity of resources, one’s success is another person’s failure. Therefore ethics search for rationally justifiable standards for the resolution of interpersonal conflict. While the realities of human life have given rise to the concepts of property, justice and scarcity, the management of scarcity requires the exercise of choice, since having more of some goods means having less of others. Exercising choice in turn involves comparisons, and comparisons are based on principles. As ethicists, the meaning of these principles must be sought in the moral basis that implementing them would require. For instance, if the implementation of distributive justice in healthcare is founded on the basis of welfare-based principles, as opposed to say resource-based principles, it means that the health system is motivated by the idea that what is of primary moral importance is the level of welfare of the people. This means that all distributive questions should be settled according to which distribution maximises welfare. Utilitarianism is fundamentally welfarist in its philosophy. Application of the principle to healthcare requires a prior understanding of the welfarist theory as expounded by the economist. Conceptually, welfarist theory is built on four tenets: utility maximisation, consumer sovereignty, consequentialism and welfarism. Utility maximisation embodies the behavioural proposition that individuals choose rationally, but it does not address the morality of rational choice. Consumer sovereignty is the maxim that individuals are the best judge of their own welfare. Consequentialism holds that any action or choice must be judged exclusively in terms of outcomes. Welfarism is the proposition that the “goodness” of the resource allocation be judged solely on the welfare or utility levels in that situation. Taken together these four tenets require that a policy be judged solely in terms of the resulting utilities achieved by individuals as assessed by the individuals themselves. Issues of who receives the utility, the source of the utility and any non-utility aspects of the situation are ignored.

#### B] No intent-foresight distinction for governments – deliberating over an action requires analysis of foreseen consequences which could be prevented which makes them intrinsic to state action

#### C] Governments aren’t singular rational agents which makes theories about individuals irrelevant – only consequentialism solves by analyzing ends divorced from an actor

### Offense

#### **Despite challenges, pharmaceutical R&D shows signs of growth.**

Terry and Lesser 21. [Colin is a Partner in our Life Sciences practice. He has been with Deloitte since 2011 working in the US firm, until 2014 when he moved to the UK practice. Colin’s client advisory work in the Life Sciences sector ranges across strategy and operations focused on the R&D function including operating model development and implementation as well as post-merger integration (PMI). These engagements have been serving client Boards and their senior leadership teams in R&D, Commercial and Supply Chain. Neil is a principal with Deloitte Consulting LLP in the Life Sciences strategy practice and a leader in the Research & Development strategy practice. He joined Deloitte in 1998 and works with life sciences executives creating and implementing strategies that drive productivity, efficiency, and value. He leads strategy, operating model design, productivity improvement, and large transformation initiatives within R&D and Regulatory Affairs. Neil is a frequent writer and speaker on R&D productivity.] May 2021. Deloitte. “Seeds of Change: Measuring the return from pharmaceutical innovation 2020.” Accessed 19 September 2021. <<https://www2.deloitte.com/content/dam/Deloitte/uk/Documents/life-sciences-health-care/deloitte-uk-measuring-the-return-from-pharmaceutical-innovation-2021.pdf#page=6>> //MHES

IRR – Internal Rate of Return

Breakthrough advances in science and technology continue to fuel innovation in the biopharmaceutical (biopharma) industry and shape health care. However, though biopharma R&D is under mounting pressure, this year's analysis is showing a potential for growth with our cohort seeing small improvements in returns on pharmaceutical innovation. Nevertheless, peak sales remain at much lower levels than in 2013, despite a small uptick this year, and R&D costs continue to increase. Costs are increasing due to the growing complexity of development and longer cycle times. There is a pressing need to optimise processes and fundamentally change the drug development paradigm through use of digital and transformative approaches. COVID-19 has spurred on these changes and the industry is well-positioned to build on the momentum and look optimistically for a future with higher returns on pharmaceutical innovation. Since 2010, our series of reports on Measuring the return from pharmaceutical innovation have provided insights into the state of biopharma R&D, by projecting the internal rate of return (IRR) on investment that 12 large-cap biopharma companies might expect to achieve from their late stage pipelines. In 2015, we added an extension cohort of four more specialised companies and backtracked their R&D investments to 2013. Over time, our analysis has shown that both cohorts have seen large declines in their expected returns, and there has been convergence in the performance of the original and extension cohorts. Moreover, for the first time since our research began, a company in the original cohort acquired an extension cohort company. For these reasons, and for the purpose of this and future reports, we have combined the original and extension cohorts to create a combined cohort of 15 companies. However, since this is a transition report, we also provide a comparative analysis of the performance of the separate cohorts. It should be noted that our analysis period was from May 2019 to April 2020 and, therefore, this report's pipeline of late-stage assets does not fully reflect the COVID-19 vaccines and therapies that have since emerged. Measuring the return from pharmaceutical innovation For the first time since 2014, the average IRR has had an uptick from the previous year, showing signs of a potential reversal in the declining trend. In 2020, the projected internal rate of return (IRR) for the combined cohort was 2.5 per cent, 0.9 percentage points higher than in 2019 but 3.9 percentage points lower than in 2013. The range between top and bottom performers narrowed from 2019 and was the third-lowest since 2013. While ten of the 15 biopharma companies in the combined cohort improved their average IRR from 2019, all but one are below the industry cost of capital. The projected IRR for the original cohort in 2020 was 1.7 per cent - an increase of 1 percentage point from 2019, but a decrease of 3.1 percentage points since 2013. The three company extension cohort, in contrast, had a projected IRR of 6.6 per cent in 2020, up from 5.2 per cent in 2019 but well below the 17.4 per cent achieved in 2013.

#### High risk nature of pharmaceutical R&D means patents are necessary to attract investments.

**Grabowski et al 15.** [Henry G. Grabowski is a professor of economics at Duke University, in Durham, North Carolina.

Joseph A. DiMasi is director of economic analysis at the Tufts Center for the Study of Drug Development, Tufts University, in Boston, Massachusetts. Genia Long is a senior advisor at the Analysis Group, in Boston, Massachusetts.] February 2015. Health Affairs, vol. 34, no. 2. “The Roles Of Patents And Research And Development Incentives In Biopharmaceutical Innovation.” Accessed 16 September 2021. <<https://www.healthaffairs.org/doi/10.1377/hlthaff.2014.1047>> //MHES  
The essential rationale for patent protection for biopharmaceuticals is that long-term benefits in the form of continued future innovation by pioneer or brand-name drug manufacturers outweigh the relatively short-term restrictions on imitative cost competition associated with market exclusivity. Regardless, the entry of other branded agents remains an important source of therapeutic competition during the patent term.  Several economic characteristics make patents and intellectual property protection particularly important to innovation incentives for the biopharmaceutical industry. 5 The R&D process often takes more than a decade to complete, and according to a recent analysis by Joseph DiMasi and colleagues, per new drug approval (including failed attempts), it involves more than a billion dollars in out-of-pocket costs. 6 Only approximately one in eight drug candidates survive clinical testing. 6  As a result of the high risks of failure and the high costs, research and development must be funded by the few successful, on-market products (the top quintile of marketed products provide the dominant share of R&D returns). 7,8 Once a new drug’s patent term and any regulatory exclusivity provisions have expired, competing manufacturers are allowed to sell generic equivalents that require the investment of only several million dollars and that have a high likelihood of commercial success. Absent intellectual property protections that allow marketing exclusivity, innovative firms would be unlikely to make the costly and risky investments needed to bring a new drug to market.  Patents confer the right to exclude competitors for a limited time within a given scope, as defined by patent claims. However, they do not guarantee demand, nor do they prevent competition from nonidentical drugs that treat the same diseases and fall outside the protection of the patents.  New products may enter the same therapeutic class with common mechanisms of action but different molecular structures (for example, different statins) or with differing mechanisms of action (such as calcium channel blockers and angiotensin receptor blockers). 9 Joseph DiMasi and Laura Faden have found that the time between a first-in-class new drug and subsequent new drugs in the same therapeutic class has been dramatically reduced, from a median of 10.2 years in the 1970s to 2.5 years in the early 2000s. 10 Drugs in the same class compete through quality and price for preferred placement on drug formularies and physicians’ choices for patient treatment.  Patents play an essential role in the economic “ecosystem” of discovery and investment that has developed since the 1980s. Hundreds of start-up firms, often backed by venture capital, have been launched, and a robust innovation market has emerged. 11 The value of these development-stage firms is largely determined by their proprietary technologies and the candidate drugs they have in development. As a result, the strength of intellectual property protection plays a key role in funding and partnership opportunities for such firms.  Universities also play a key role in the R&D ecosystem because they conduct basic biomedical research supported by sponsored research grants from the National Institutes of Health (NIH) and the National Science Foundation (NSF). The Patent and Trademark Law Amendments Act of 1980 (commonly known as the Bayh-Dole Act) gave universities the right to retain title to patents and discoveries made through federally funded research. This change was designed to encourage technology transfer through industry licensing and the creation of start-up companies. Universities received only 390 patents for their discoveries in 1980, 12 compared to 4,296 in 2011, with biotechnology and pharmaceuticals being the top two technology areas (accounting for 36 percent of all university patent awards in 2012). 13

Fiscal incentives key to preparedness against emerging threats—bioterror, antimicrobial resistance, and new infectious diseases.

Marjanovic PhD and Feijao PhD 20. [Sonja Marjanovic directs RAND Europe’s portfolio of research in the field of healthcare innovation, industry and policy. Her work provides decisionmakers with evidence and insights to support innovation and improvement in healthcare systems, and to support the translation of innovation into societal benefits for healthcare services and population health. Carolina Feijao is an analyst working in the areas of science and emerging technology at RAND Europe. Previously, she worked for Frontiers, an Open Access scientific publisher, where she led the launch of and managed three peer-reviewed journals: Sustainable Food Systems, Forests and Global Change and Sustainable Cities. She gained experience in policy making through a placement at DEFRA and she has been a research associate for GenPol, a Cambridge-based think tank focusing on gender equality issues. She also participated in the Management of Technology & Innovation Programme at Cambridge Judge Business School and carried out consulting projects ranging from market entry strategies for a plant breeding company to pitching a business proposal on innovative wound dressing products.] 2020. RAND Corporation. “Pharmaceutical Innovation for Infectious Disease Management: From Troubleshooting to Sustainable Models of Engagement.” Accessed 19 September 2021. <https://www.rand.org/content/dam/rand/pubs/perspectives/PEA400/PEA407-1/RAND\_PEA407-1.pdf> //MHES

Pharma is mobilising substantial efforts to rise to the COVID-19 challenge at hand. However, we need to consider how pharmaceutical innovation for responding to emerging infectious diseases can best be enabled beyond the current crisis. Many public health threats (including those associated with other infectious diseases, bioterrorism agents and antimicrobial resistance) are urgently in need of pharmaceutical innovation, even if their impacts are not as visible to society as COVID-19 is in the immediate term. The pharmaceutical industry has responded to previous public health emergencies associated with infectious disease in recent times – for example those associated with Ebola and Zika outbreaks.11 However, it has done so to a lesser scale than for COVID-19 and with contributions from fewer companies. Similarly, levels of activity in response to the threat of antimicrobial resistance are still low.12 There are important policy questions as to whether – and how – industry could engage with such public health threats to an even greater extent under improved innovation conditions. The COVID-19 pandemic is a game-changer among global public health threats. The risk to human life (both in terms of morbidity and quality of life), the economic risks, the epidemiology of the disease and speed of escalation have led to a crisis-response by many governments around the world. This has in turn influenced the immediate industry efforts. Many other infectious disease threats may not manifest as crises in the short term and in the same way as COVID-19, but they could nevertheless escalate. They are not considered to be crises from a short term perspective because they are contained to specific regions and affect fewer people at present – or are re-emerging (e.g. Ebola) – or their impacts have not yet materialised at a scale that would qualify as an immediate crisis (e.g. growing risks of antimicrobial resistance to some infectious pathogens). However, such diseases and issues are recognised as global threats that could become crises in the future.13 The emerging threats raise important policy questions about how government and the pharmaceutical industry can work together to ensure that pharmaceutical industry innovation is incentivised sustainably and at scale. This is important to help mitigate against current and emerging threats becoming crises further down the line. At present, there are no clear and specific criteria to determine when a disease can trigger the types of healthcare-innovation-related policy actions that have been deployed in response to the COVID-19 crisis. For example, this applies to criteria for securing financial resources for innovation-related activities, reforming regulation to accelerate trials and regulatory approval processes, and securing reimbursement mechanisms that help enable industry engagement and the search for rapid solutions. The WHO guidance on what constitutes a pandemic phase does provide guidance on national policy response options, but not specifically as they relate to healthcare innovation activity.14 There are also questions as to whether such policy initiatives and incentives should only be applied in crisis situations, or also as part of proactive government and industry efforts to innovate in the areas of public health threats in order to prevent future global calamities. A crisis and ‘emergency mode’ response may be inevitable for some diseases, but more can be done to mitigate against the need for such a response – especially in cases where emerging threats and their consequences can be foreseen and are known to be a risk. We need to anticipate and act now in terms of how we plan and incentivise better for the future, and how we distinguish between different types of infectious disease threats and phases in framing incentives and regulation. Innovative financial instruments must be integral to any sustainable and scalable approach to incentivising pharmaceutical innovation for tackling emerging threats to public health from infectious diseases The pharmaceutical industry has a responsibility to both its shareholders and to society at large. Incentivising the pharmaceutical industry to innovate solely on the grounds of being a socially responsible sector is unlikely to lead to a sustainable and scalable approach for innovating in response to emerging infectious disease threats. There are also potential challenges to the types of innovation (i.e. how radical or incremental) a reliance on incentives rooted solely in a social responsibility argument can lead to. Donating existing compounds for testing is important, but it is different to at-scale, industry-wide intensive investment in R&D geared at developing highly innovative diagnostics, medicines and vaccines. Even in the case of COVID-19, there are significant differences in the scale of innovative activity that focuses on repurposing existing products and technologies – for example, through testing existing antiviral compounds for potential therapeutic value – and more radically innovative R&D efforts aimed at developing something that acts on the COVID-19 virus in fundamentally novel ways.

#### Bioengineered diseases cause extinction.

Millett/Snyder-Beattie 17 [Piers Millet is a Consultant for the World Health Organization, PhD in International Relations and Affairs, University of Bradford, Andrew Snyder-Beattie previously spent five years at the Future of Humanity Institute (University of Oxford), where he worked as a program manager and later as Director of Research, developing programs across the institute including those in biosecurity and systemic risk. Prior to that, he was a researcher at a personalized medicine startup. He holds a PhD/DPhil in Zoology from the University of Oxford and is an alumnus of the Johns Hopkins Emerging Leaders in Biosecurity Initiative, “Existential Risk and Cost-Effective Biosecurity”, Health Security, Vol 15(4), http://online.liebertpub.com/doi/pdfplus/10.1089/hs.2017.0028

Historically, disease events have been responsible for the greatest death tolls on humanity. The 1918 flu was responsible for more than 50 million deaths,1 while smallpox killed perhaps 10 times that many in the 20th century alone.2 The Black Death was responsible for killing over 25% of the European population,3 while other pandemics, such as the plague of Justinian, are thought to have killed 25 million in the 6th century—constituting over 10% of the world’s population at the time.4 It is an open question whether a future pandemic could result in outright human extinction or the irreversible collapse of civilization. A skeptic would have many good reasons to think that existential risk from disease is unlikely. Such a disease would need to spread worldwide to remote populations, overcome rare genetic resistances, and evade detection, cures, and countermeasures. Even evolution itself may work in humanity’s favor: Virulence and transmission is often a trade-off, and so evolutionary pressures could push against maximally lethal wild-type pathogens.5,6 While these arguments point to a very small risk of human extinction, they do not rule the possibility out **entirely.** Although rare, there are recorded instances of species going extinct due to disease—primarily in amphibians, but also in 1 mammalian species of rat on Christmas Island.7,8 There are also historical examples of large human populations being almost entirely wiped out by disease, especially when multiple diseases were simultaneously introduced into a population without immunity. The most striking examples of total population collapse include native American tribes exposed to European diseases, such as the Massachusett (86% loss of population), Quiripi-Unquachog (95% loss of population), and the Western Abenaki (which suffered a staggering 98% loss of population). In the modern context, no single disease currently exists that combines the worst-case levels of transmissibility, lethality, resistance to countermeasures, and global reach. But many diseases are proof of principle that each worst-case attribute can be realized independently. For example, some diseases exhibit nearly a 100% case fatality ratio in the absence of treatment, such as rabies or septicemic plague. Other diseases have a track record of spreading to virtually every human community worldwide, such as the 1918 flu,10 and seroprevalence studies indicate that other pathogens, such as chickenpox and HSV-1, can successfully reach over 95% of a population.11,12 Under optimal virulence theory, natural evolution would be an unlikely source for pathogens with the highest possible levels of transmissibility, virulence, and global reach. But advances in biotechnology might allow the creation of diseases that combine such traits. Recent controversy has already emerged over a number of scientific experiments that resulted in viruses with enhanced transmissibility, lethality, and/or the ability to overcome therapeutics.13-17 Other experiments demonstrated that mousepox could be modified to have a 100% case fatality rate and render a vaccine ineffective.18 In addition to transmissibility and lethality, studies have shown that other disease traits, such as incubation time, environmental survival, and available vectors, could be modified as well.19-21

#### AMR is an existential threat, it’s nonlinear, and has an invisible tipping point

Silverman ’16 (Rachel Silverman – MPhil with Distinction in Public Health @ the University of Cambridge, Senior Policy Analyst and Assistant Director of Global Health Policy @ the Center for Global Development, focusing on global health financing and incentive structures, “Confronting Antimicrobial Resistance: Can We Get to Collective Action?” 19 April 2016, https://www.cgdev.org/blog/confronting-antimicrobial-resistance-can-we-get-collective-action)

Antimicrobial resistance is already causing huge harm – and the worst is yet to come. To open the panel, Dr. Chan issued a serious warning about the size and scope of the AMR threat: “everyone will be affected if we do not address this problem.” AMR is already responsible for an estimated 700,000 global deaths each year, 50,000 of which take place in the US and Europe. Extensively drug-resistant (XDR) tuberculosis—cases where the most effective first- and second-line drugs are rendered useless—infected an estimated 47,000 people worldwide in 2014, only one ‘last-line’ antimicrobial is available to reliably treat gonorrhea, and few new antimicrobial drugs are in the development pipeline. According to the latest review, AMR could cause 10 million deaths each year by 2050, with knock-on effects draining many trillions from the global economy. Summers suggested that AMR and potential pandemics, alongside climate change and nuclear proliferation, represent the top three existential threats to life on earth as we know it. And as Dr. Chan explained, the worst-case scenario implies the end of modern medicine as we know it. Even worse, Summers suggested that AMR seems like a “quintessential non-linear phenomenon, and therefore more dangerous.” Year by year the effects are small and mostly invisible. But at some point in the future they could suddenly become catastrophic, like a “levee that doesn’t hold and unleashes a flood.” Dr. Chan concurred that “the tipping point is not predictable because…microbes are invisible. We don’t even know when they’re going to make the switch” to become resistant to existing drugs. Antimicrobial efficacy is a global public good threatened by serious market failures.

## Case