COMPREHENSIVE REVIEW

The transition from inquiry to evidence to actionable clinical knowledge: A proposed roadmap

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Abstract

Rationale, aims, and objectives: We consider the question "What should we do?" in the context of clinical research/practice. There are several steps along the way to providing a satisfactory answer, many of which have received considerable attention in the literature. We aim to provide a unified summary and explication of these "steps along the way". The result will be an increased appreciation for the meaning and structure of "actionable clinical knowledge".

Methods: We review the literature to identify pertinent works dealing with evidence production and translation into actionable clinical knowledge. We draw from insights in this literature about various aspects of reasoning relevant to clinical questions and integrate these into a unified approach to the processes that lead to actionable clinical knowledge.

Results: We collect, collate, and integrate some of the work by Bauer, Carper, Goldman, Haack, McHugh and Walker, and Upshur and colleagues and obtain guidelines to aid in the evidence-to-actionable-clinical- knowledge transition.

Conclusions: Clinical decision-making is not infallible, and the steps we can take to minimize error are context dependent. Medical evidence, produced as it is by human effort, can never be perfect. We will be doing well by assuring that the evidence we use has been produced by a reliable process and is relevant to the question posed.

KEYWORDS
evidence-based-medicine, Fallibilism, eclecticism, pluralism, reliabilism, translational research

1 | INTRODUCTION

> It is error only, and not truth, that shrinks from inquiry.
> Thomas Paine

We are seeking "actionable clinical knowledge". By this we mean the amount and kind of knowledge necessary for us to reasonably proceed with a course of treatment in a clinical setting. We first argue that our quest can be taken to start with a question: A question like "What shall we do?" in the context of clinical-decision-making. We then assemble relevant and reliable evidence which can be used to answer the question. Finally, we assess whether the evidence so assembled constitutes "actionable clinical knowledge". In short, we study the I → E → ACK transition.

1.1 | Inquiry

According to standard dictionary accounts, to inquire is to ask a question; to request information; to conduct a study; to investigate. When inquiring, then, one is seeking knowledge about some specified entity, topic, concept, or idea. The present paper focuses on questions of the form "What shall we do?" in the context of clinical decision-making. We argue that whatever the make-up of clinical research/practice might be, the process usually starts with a question. This hardly incurs any loss of generality: Even, when for technical reasons one is presented with a statement (eg, the null hypothesis may be that *The mean responses to the drug and placebo are equal)*, what is really of interest is the answer to a question (eg, *Is the drug more effective than the placebo?*).

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1.2 | Evidence

Often, the first step in providing an answer is searching for some relevant evidence/information that may be used for this purpose. Sometimes such evidence exists; sometimes further research is required before the evidence is both reliable enough for, and relevant to, the problem in hand. This is not as easy as it may sound, and we begin our catalogue of the difficulties encountered on the road to actionable clinical knowledge by citing Haack.[1]

> *"Sometimes scientists know that they don't have all of the evidence relevant to a question; and sometimes they have a pretty shrewd idea what the evidence is that they don't have. But sometimes, given the evidence they have, they may be unable to judge, or may misjudge, whether or what additional evidence is needed. They can't always know what it is that they don't know; they may not, at a given time, have the vocabulary to ask the questions answers to which would be relevant evidence. Nor can they always envision alternative hypotheses which, if they did occur to them, would prompt them to revise their estimates of the supportiveness of their evidence. And so on. Since evidential quality is not transparent, and scientists can only do the best they can do, a scientist may be reasonable in giving a claim of degree of credence which is disproportionate to the real, objective quality of his evidence, if that real quality is inaccessible to him. Reasonableness, so understood, is perspectival".* (77)

This quote sets the tone for much of which is to follow. In particular, it links the answering of a question to the gathering of evidence and the difficulty in assessing the quality of evidence gathered and determining whether additional evidence may be needed (as in the example of the Salk polio vaccine, described below). It recognizes that evidence, gathered and evaluated as it is by human effort, is fallible, and whether it may be regarded as a reasonable guide to guide clinical decision-making, depends on the circumstances.

The overall process proceeds as illustrated in Figure 1. It is noteworthy that the process does not necessarily end at the point at which reliable relevant knowledge is reached. Rather, it is recognized that such knowledge will often lead to further questions. Indeed, asking a question can lead to other questions directly. If the short answer to a question is to conduct a clinical trial, one immediately has to ask details about the trial: Why (superiority vs equivalence, explanatory vs pragmatic)? On whom? Compared to who? For how long? What outcome(s) will be measured? How?, etc.

1.3 | Actionable clinical knowledge

More details concerning the forming of questions, the evaluation of evidence and the steps involved in arriving at actionable clinical
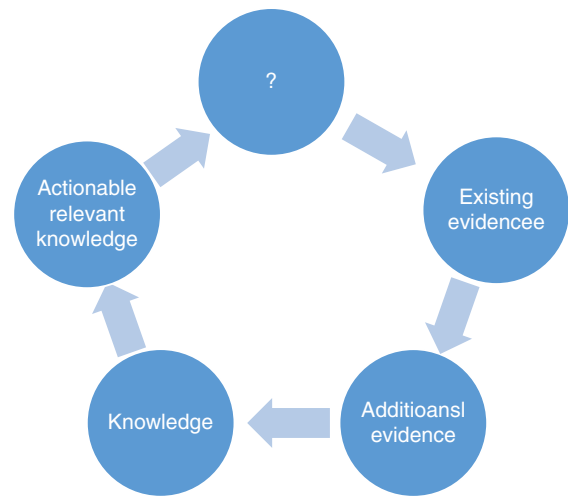

FIGURE 1 Answering a question. The evidence to knowledge transition is of special importance, and is unpacked in the text

knowledge are shown in Figure 2 where Bauer's "The Knowledge Filter" is represented.[2] At the top of the filter is a sampling of "all human traits", anyone of which can give rise to a question to which an answer will be sought. These include such things as wild ideas, hunches, conventional wisdom, jealousy, ignorance, incompetence, ambition, etc., etc. The questions that arise and their tentative answers are then passed through a series of filters, each filter eliminating certain kinds of question/answer couples that cannot give rise to reliable, objective knowledge. The first, coarsest filter eliminates answers to questions that are nonsense, reflect stupidity or are pseudo-scientific. There are also limits to the *kinds* of questions that can be asked, for example, ethical constraints. Those that remain are called "frontier science" to reflect the fact that these have only passed over the lowest bar in the way to objective, reliable knowledge. The next filter is designed to wash-out bias, error, and dishonesty. This represents the "can this get published?" stage where, for example, editors and referees evaluate the claims made. The residuals have made it to the "primary literature" where most of what appears is not obviously wrong, and might even be right. Next stop is the "secondary literature" where mistakes, uninteresting stuff, and fraud are eliminated and what remains are review articles and monographs that are mostly reliable. Textbooks are next where Q/As that are either mistaken or obsolete are eliminated. These are termed mostly very reliable. Finally, over time, the filtering process arrives at textbooks of the future, thought to contain reliable, objective knowledge in that what they present has further refined "mostly very reliable" information, integrated it with other, relevant knowledge, and has been shown to "work well." This comprises "actionable clinical knowledge". Further discussion and examples are provided by Haack.[1(196ff)]

Thus, given a question, the Knowledge Filter depicts a series of ways in which one gets to arrive at an actionable answer. The filter is shown working on questions that arise in a formal, academic context
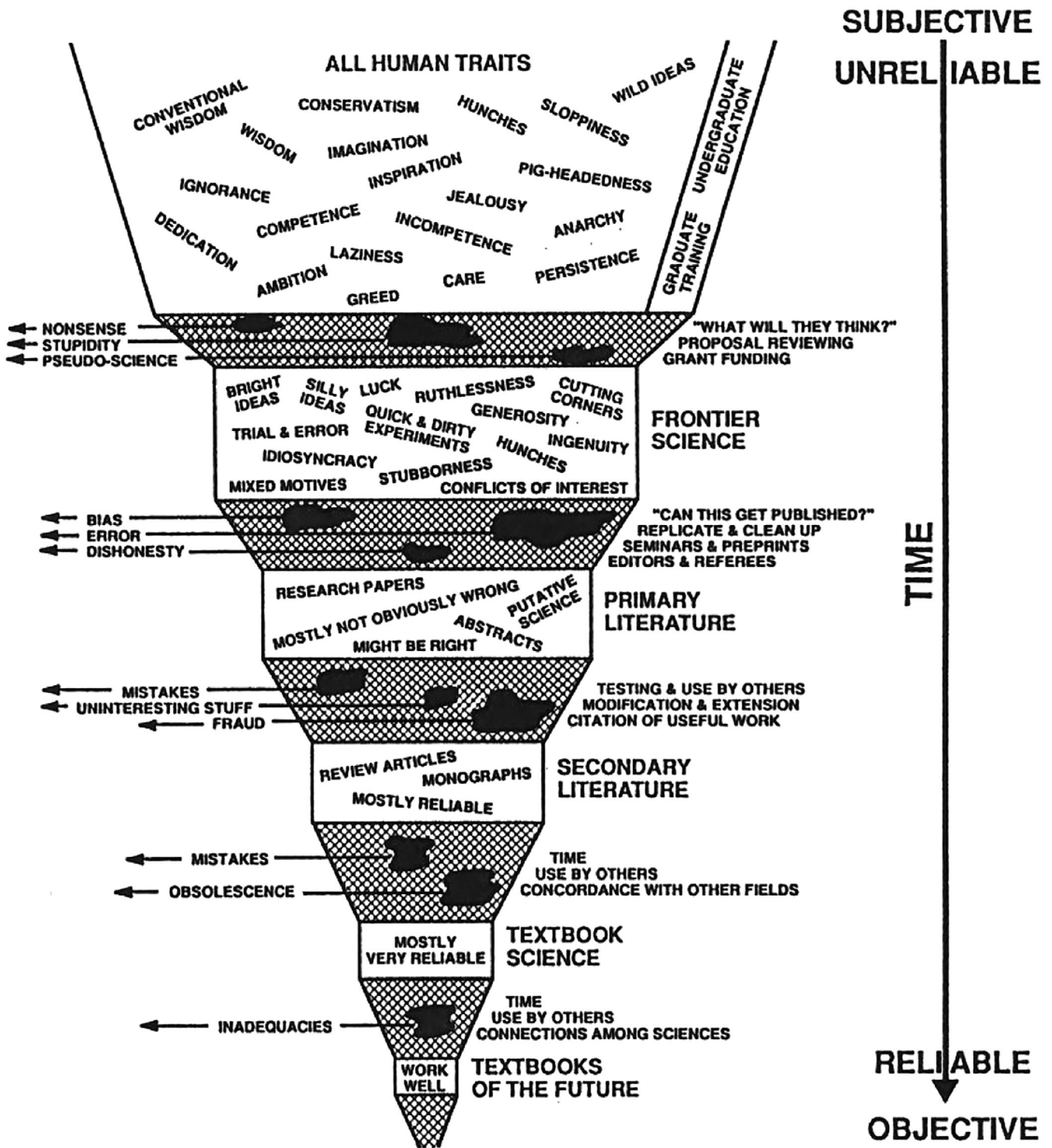
FIGURE 2 Bauer's "Knowledge filter"

where answers are pursued and developed via the publication process. This is but one way at arriving at actionable clinical knowledge. Other "ways of knowing" are possible and worthy of mention. Some of these are considered in the next section.

2 | WAYS OF KNOWING

The International Baccalaureate (IB) offers four international educational programs to more than one million students in over

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146 countries (www.ibo.org). They distinguish between eight different ways of knowing, viz.

- Language,
- Sense perception,
- Emotion,
- Reason/Logic,
- Imagination,
- Faith,
- Intuition, and
- Memory.

It should not be necessary to expound on each of these ways (though the IB does). Every reader of this journal will have an appreciation for the role each plays in approaching the answer to a given question. It is perhaps enough to mention that there are no surprises: Each pretty much is defined in the natural way. Regarding Bauer's Knowledge Filter, all eight are included in the top layer of the filter comprising "all human traits". For example, "wild ideas" might result from some combination of imagination, faith, intuition, memory and/or emotion. The finer layers of the filter will rely more on sense perception, language and reason/logic. We might also mention that the items in the list are nor meant to be interpreted narrowly. For example, "language" encompasses the use of analogy, which has been called "the fuel and fire of thinking" by Hofstadter and Sander.[3] It clearly also includes scientific literature in its entirety, all primary, secondary literature as well as textbooks, monographs, etc.

Another, more condensed inventory of "ways of learning" developed explicitly for the development of clinical knowledge, was given by Carper.[4] Her typology consists of four ways of knowing:

- Personal knowledge used in practice that is based on past experiences, beliefs, attitudes, and biases; knowledge needed to engage in authentic interpersonal relationships;
- Empirical knowledge derived from scientific systematic inquiry;
- Ethical knowledge based on standards, values, moral reasoning, and ethical frameworks; what to do and what not to do; and
- Aesthetic clinical practice based on art, the subtle craft of practice in action based on perception and empathy.

It is important to note that there is no requirement to choose one and only one way of knowing. Depending on the question asked, some subset of these may suffice, but generally all four will be required in the clinical decision - making- process. And, often, which of the four is emphasized will change as the process evolves. Thus, improvisation is seen as an important ingredient in arriving at actionable clinical knowledge, generally refined as a clinician becomes experienced over time.[5]

Carper's list has caused some confusion in that the four "ways of knowing" seem to refer to "what is known", not to how one came to acquire this knowledge. Silva et al[6] noted that "ways of knowing" suggests a process - how one comes to know - yet the patterns are depicted as four end-products: personal knowledge, empirics, ethics,

and aesthetics. This seems to leave open the question: How does one come to know the knowledge that is empiric, aesthetic, personal, or ethical? They suggest that this represents a shift from epistemology to ontology (their title begins: "From Carper's patterns of knowing to ways of being") which is certainly something that needs to be guarded against. However, one need not trespass the boundary of epistemology here: Carper maintained a strictly epistemological bent and similar terms are being used to describe both ways of knowing and the sorts of evidence these ways produce. The particular methods that will be used to acquire certain types of evidence (eg, one might use questionnaires or interviews to gather personal data) will need to be specified in specific cases, but one need not assume that what one may learn is free from bias and an error-free reflection of the true personal attribute being assessed.

Carper's ways of knowing are considered further below. For now, we note that these ways are available to be employed to produce evidence upon which an answer to the question posed will be formulated. A look at the Knowledge Filter (Figure 2) shows that evidence provides increasing justification for the proposed answers to the question being considered. In particular, it is seen that justification comes in degrees.

3 | EVIDENCE

We focus on the types of evidence identified as pertinent to clinical practice by Upshur et al,[7] hereafter referred to as UVG Evidence. Four kinds of evidence are distinguished, viz.,

- Qualitative-personal,
- Qualitative-general,
- Quantitative-general, and
- Quantitative-personal

All of the UVG dimensions of evidence, as well as medical evidence in general, has certain characteristics. These characteristics of medical evidence were identified as follows by Upshur[8]

- Provisional,
- Defeasible,
- Emergent,
- Incomplete,
- Constrained,
- Collective, and
- Asymmetric

Upshur argues that the provisional, defeasible and emergent properties of evidence show that the ultimate structure of medical evidence is fallibilistic. Fallibilism holds that any of our opinions or beliefs about the external world may turn out to be false and that a large cloud of uncertainty shadows our deliberations. The incomplete and constrained properties of evidence show that medical evidence is under-determined. Under-determination holds that mutually

incompatible, but still internally consistent, explanations can be provided for the same evidence. The collective dimension of evidence indicates that the production, interpretation, dissemination and implementation of evidence is a social process, subject to the forces and vagaries of social life. Haack[1] adds

> "*Scientific inquiry is fallible … and judgements of better- and worse-conducted inquiry, like judgements of the worth of evidence, are perspectival, dependent on background beliefs*" (100).

If one then views medical evidence as fallible, under-determined and socially produced, this suggests that one adopt a properly humble position as regards its use in guiding clinical decision-making. This unassuming posture is not meant to preclude action, but rather to eliminate over-confidence, arrogance at the point when one is deciding which action to take. We will come to appreciate that the amount of confidence that one demands in a piece of evidence is context-dependent.

4 | THE EVIDECE-TO-KNOWLEDGE TRANSITION

> *There is no sharp line to be drawn between cases where it is, and where it is not, proper to say that a person knows something*. Susan Haack (2009, 301)

Not all evidence qualifies as knowledge, let alone actionable clinical knowledge. We begin to develop a bridge from evidence to knowledge following Haack[9(p302)] who noted that the traditional (with roots back to Plato) definition of knowledge is justified, true belief (K = JTB).[9] Formally, a subject S knows that a proposition P is true, if and only if:

P is true, and

S believes that P is true, and

S is justified in believing that P is true

That K = JTB is not without its own set of questions. The most famous criticism of K = JTB rests on the so-called Gettier counter-examples where it is shown that individuals can have a justified, true belief regarding a claim - thereby satisfying all three conditions for knowledge in the JTB account - but do not appear to be genuine cases of knowledge. One of the (two given in the original Gettier paper) examples follows: We are given that Smith has a justified belief that "Jones owns a Ford". Smith can therefore (justifiably) conclude that "Jones owns a Ford, or Brown is in Barcelona", even though Smith has no knowledge whatsoever about the location of Brown.

It turns out that, in fact, Jones does not own a Ford, but by sheer coincidence, Brown is really in Barcelona. Thus, Smith has a belief "Jones owns a Ford, or Brown is in Barcelona", that is both true and justified, but falls well short of what we normally would consider to be "knowledge".

More examples of this kind are easy to generate. Start with a proposition, P1, that, while justified, turns out to be wrong. Then take P2 to be a proposition that is not known to be either right or wrong, but that turns out to be correct. Then "P1 or P2" is justified and true, but represents only a lucky happenstance, and not any real appreciation for what is going on. Examples such as these have been criticized because of the "justified statement" that turns out to be wrong. The complaint is that one should not consider false statements to have been justified in the first place. Jennifer Nagel gives a good, detailed, and comprehensible account of the many attempts that have been made to "fix" K = JTB in response to the Gettier challenge.[10]

These examples illustrate the difficulty of settling on the very definition of *knowledge*. We believe that these problems can be best seen to arise due to the simple fact that, while knowledge is viewed as binary, justification comes in degrees, as Bauer's filter clearly illustrates. We follow Haack (2009) who, in considering problems such as these, begins by noting that while justification comes in degrees, knowledge does not. In her Chapter "'Know' is Just a Four-Letter Word" she argues that there is no way to set the degree of justification required for knowledge high enough to avoid the Gettier paradoxes without setting it so high as to lead to scepticism. She then considers a number of alternatives to K = JTB, starting with requiring that justification requires truth, that is, you can be justified in believing P only if P is true, through justification requires true premises, and justification is indefeasible, justified true belief, up to knowledge requires deducibility from known premises. Having discussed seven such proposals, she notes only one precludes knowledge by luck, and that proposal allows no knowledge at all. One is then left with the problem of defining knowledge in such a way as to be useful in clinical practice.

We note that since justification comes in degrees, and since we can never achieve perfect clinical knowledge, one can only aim for doing the best that one can do given our human limitations. The following definition reflects these considerations: *Knowledge is justified belief, and one's belief is justified to the extent that s/he has good (relevant) evidence to support it*. Recalling that medical evidence is itself never perfect, it follows that beliefs are never fully justified, and hence that medical knowledge is imperfect. Acquiring knowledge is a human activity and is constrained by human limitations. The best that one can hope to achieve is that the evidence one has been obtained through a reliable process. Rather than justification, all that is required that the belief be the result of a reliable process.

The resulting theory of justification and knowledge is known as *Reliabilism*, which holds that a subject S knows that a proposition P is true, if and only if:

P is true, and

S believes that P is true, and

S has arrived at the belief that P through some reliable process.

So - S has a justified belief in P if and only if the belief is the result of a reliable process. We say that we have knowledge of P, then, if and only if our belief in P is based on a reliable process.

Goldman[11] is perhaps the most influential proponent of reliabilism. Goldman (1967) responded to Gettier by arguing that knowledge is true belief caused in an appropriate way. Goldman at

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first left the notion of "appropriate" open-ended, but then provided a substantive account of justification by reference to reliable, that is, truth-conducive, belief-forming processes. Further examples and discussion are provided by Nagel.[10]

5 | KNOWLEDGE

We focus on knowledge that is pertinent to clinical practice. A useful taxonomy of types of such knowledge was given by McHugh and Walker.[12] They distinguished between four types of knowledge (hereafter, MW knowledge), viz.,

- Tacit-particular,
- Tacit-general,
- Explicit-general, and
- Explicit-particular

These are directly related to UVG evidence types as was shown by Kowalski et al.[13] UVG evidence becomes MW knowledge if the evidence is both reliable and relevant to the question posed.

The various conceptual models/typologies examined thus far (UVG, MW, and Carper) can be viewed as complementary. While terms and emphases vary across the models to some degree, they all incorporate evidence for clinical practice that is derived both through systematic scientific methods and personal qualitative experiences. These models are intimately related, for example, Carper's[4] ways of knowing are related to UVG evidence and MW knowledge (Read ">>>" as "can lead to") as follows:

- Carper's "personal way of learning">>> UVG qualitative evidence >>> MW tacit knowledge
- Carper's "empirical way of learning">>> UVG quantitative evidence >>> MW explicit knowledge
- Carper's "ethical way of learning" recognizes one of the Upshur-constraints on evidence (and therefore knowledge). Another, perhaps less obvious, constraint is the limited applicability of quantitative/general evidence to quantitative/particular questions (viz., Do the results of this clinical trial apply to my patient?).
- Carper's "aesthetic way of learning" is said to integrate the other types of knowing. It recognizes that while the first three ways of knowing are separable, they overlap and interact in ways that may create a deeper appreciation for the phenomenon in question via perception, feeling, sensing, all of the human tools that humans use to make sense of their existence. This allows us to relate Carper's WoK to the IB's WoK. It also explicitly calls out "human tools", thereby recognizing all of our inherent human limitations.

One area of potential criticism in each of the models is the emphasis on personal or qualitative components emphasized in varying degrees when compared to components that are scientifically derived through systematic methods. We believe that we have addressed this concern above where it was pointed out that *both* objective and subjective sources of data need to be tapped to appreciate clinical problems in their entirety. We reiterate: It is important to recognize that not all aspects of the illnesses presented by patients can be managed with evidence in a standardized way.[14] Generally, clinicians all recognize the importance and therapeutic elements of personal human connections in all clinician/patient interactions. Each of these models represent those elements to varying degrees and capture what is often described as the art and science of clinical practice.

Our objective has been to produce "an increased appreciation for the meaning and structure of actionable clinical knowledge". As an example of what sorts of insights this increased appreciation can provide, we consider the purported research/practice distinction. While many believe that there is a clear distinction between clinical research and clinical practice, we have previously argued that the distinction is illusionary.[15] Here we approach the research/practice distinction using just the concepts developed above. Research produces evidence. This will be of one (or more) of the UVG types. This may become actionable clinical knowledge (MW knowledge) if it is both reliable and relevant to the problem in hand. Thus,

UVG evidence/MW knowledge = Research/Practice

McHugh and Walker[12(p577)] explain this relationship as follows.

> "*Knowledge can be described along two intersecting 'dimensions': the tacit-explicit and the particular-general. These dimensions supersede the familiar 'objective-subjective' dichotomy, as they more accurately describe the relationship between medical science and medical practice*".

6 | THE TRANSITON FROM INQUIRY TO ACTIONABLE CLINICAL KNOWKEDGE

Having asked a question of the form "What shall we do?" in the context of clinical practice/research, the transition from that inquiry to actionable clinical knowledge has proceeded as shown in Figure 3.

Figure 3 has an important caveat. It depicts the I → E → ACK transition as proceeding smoothly from inquiry to action without incident. First, we should recognize that some models of clinical reasoning include iterative reasoning as well so that the arrows shown can go in both directions (as when, eg, available evidence helps to determine the question(s) asked). However, even after taking this into consideration, there will be bumps along the way. No matter how well thought out in advance, there will be surprises. We next review the "steps along the way" and some of the obstacles encountered on the road to actionable clinical knowledge. It needs to be realized that, at each step, multiple problems are apt to be encountered. We do not attempt an exhaustive inventory; rather, we point to what seems to us to be one of the more important obstacles to be faced at each point.

The fundamental problem is that, at every step, human beings are making decisions... and such decisions are influenced by a number of factors unrelated to scientific considerations. For example,
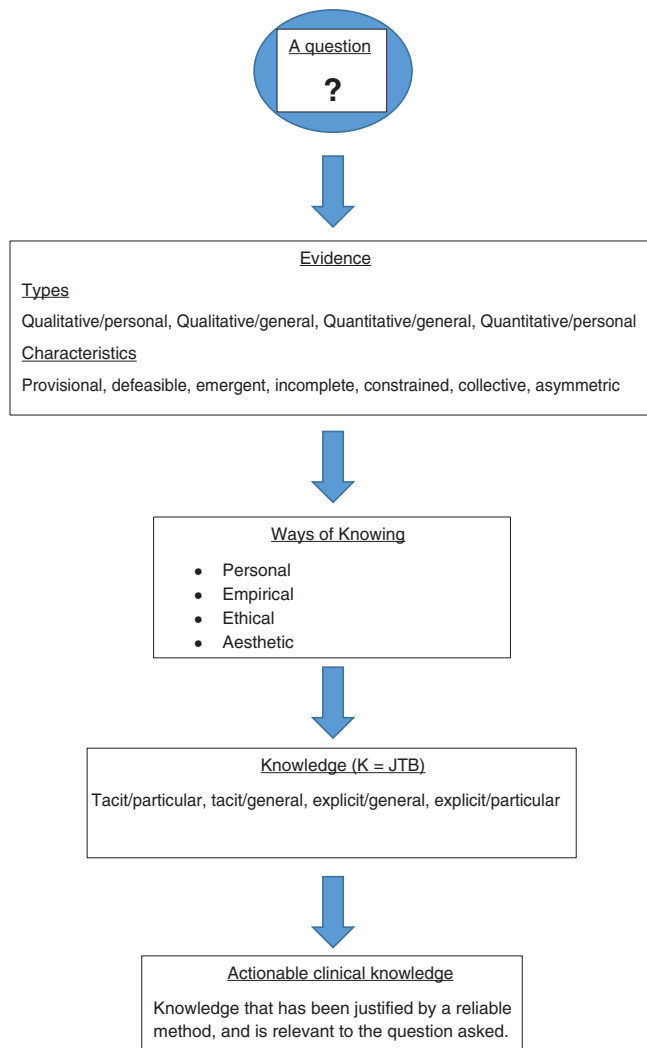
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FIGURE 3 The inquiry to actionable clinical knowledge transition

FDA requirements fluctuate with those appointed as Commissioner, and political pressures can result in significant changes in the criteria used.

The first hurdle to be faced is that of choosing what question to answer.

> "An approximate answer to the right problem is worth a good deal more than an exact answer to an approximate problem". ~ John Tukey

The first step in the process depicted in Figure 3 is especially important. The form, content, structure and specificity of the question posed strongly influences which way(s) of knowing are apt to be most fruitful in arriving at a satisfactory answer. These ways will, in turn, point to sources of evidence that can be used for this purpose. And so on. A familiar example involves the distinction between explanatory and pragmatic clinical trials. These types of trials ask different questions (their *aims* are different: understanding vs decision-making) and this effects everything about the trial.[16]

It should be clear that one can stumble in a number of ways at this early stage in the process. We focus on one that appears at first glance to be not a problem at all. Successful scientists (those receiving funding) are those who have learned to pose questions that they can answer, and that the answer will be of interest (value) to the sponsor. This short-term reward to the funded scientist may, however, be but a symptom of a longer-term serious problem. To see how, consider the "tools to theories" idea developed by Gigerenzer[17]: "ways of organizing data that begin as technical tools have a habit of becoming the very premises of the theories that seek to explain that organization" (435). This was also emphasized by Lewontin[18]: "The problems on which geneticists work have become those that can be answered from DNA sequences (128) ... "A single easily acquired technique changed and pauperized, temporarily it is to be hoped, an entire field of study" (129). "Scientists pursue precisely those problems that yield to their methods" (72-3) ... "Science as we practice it solves those problems for which its methods and concepts are adequate, and successful scientists soon learn to pose only those problems that are likely to be solved" (73).

In such situations, the I → E → ACK diagram would have to be amended to allow the first arrow to point in both directions. However, we believe this *trend* needs to be reversed. Rather than finding jobs to fit the tool, we should identify those jobs most in need of doing, and then select the appropriate tool. If a DNA sequence turns out to be that tool in a particular case, so be it. But tool selection should follow from job specifications, not dictate them. We argue for a "horses for courses" approach.[19,25] As explained and illustrated by Pettigrew and Roberts, this is not just a catchy aphorism without important implications for the ways in which clinical research is properly conducted. In brief, "horses for courses" is another way of saying "pick the right tool for the job". A hammer may be best for driving a nail, but there are better ways to fasten a screw. RCTs may be best to establish efficacy, but observational studies are a better way to assess long-term safety concerns.[17] The market may be the best way to decide certain questions, but it cannot be best for all the questions that need be answered in designing and achieving effective and equitable health care structures.[26]

6.1 | Ways of knowing

We advocate for an "All hands on deck" approach, limited only by the requirements that the way of knowing selected represent a reliable process, are not subject to ethical constraints, and are relevant to the question posed. Otherwise, no holds barred. No stone left unturned. Many believe that this completely open approach can - and should - be restricted further in some way. In particular, "the scientific method" will appeal to devotees of "scientism". One problem with this revolves around scientism itself.[9,10] Even more fundamentally, there is no such thing as "the scientific method". Bauer referred to "the myth of the scientific method". Haack[1(p10)] toyed with the idea of beginning her book "There is no thing such as the scientific method, and this is a book about it". We believe this puts the kibosh

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on the notion of a single methodological approach, emphasizing instead that whatever the scientific method turns out to be, it is many splendored. No one grand "theory of everything" is available. Haack also quoted Percy Bridgman as saying, "the scientific method, as far as it is a method, is nothing more than doing one's damnedest with one's mind, no holds barred" (24).

Haack also pointed out that these ideas can be traced back at least as far as Feyerbend who was among the first to advance the idea that there is no such thing as unified, universal scientific method. If believers in scientific method wish to express a single universally valid rule, Feyerabend jokingly suggested, it should be "anything goes". We take his suggestion seriously. We believe in scientific *pluralism*.[27] This is contrasted with *monism*, the thought that there is but one way to obtain "the scientific answer" to every question. The required flexibility is a function of the features specific to the particular problem and of the particular aims of the research.

6.2 | Existing evidence

> "*Nothing is more dangerous than a dogmatic worldview – nothing more constraining, more blinding to innovation, more destructive of openness to novelty*". ~ Stephen Jay Gould.

A major obstacle to be faced at this point is keeping one's mind open to the idea that there is not one, single "way of knowing" that that can be used to answer all of the many, varied questions that can arise in clinical decision-making contexts. In particular, one needs to guard against adopting the dogmatic worldview that evidence-based-medicine (EBM) provides such a window. An oft-cited early guide to the practice of EBM is Sackett et al.[23] This EBM "bible" has five chapters with titles:

1. How to ask clinical questions you can answer
2. Searching for the best evidence.
3. Critically appraising the evidence.
4. Can you apply this valid, important evidence in caring for your patient?
5. Evaluation.

These correspond, roughly, to the steps we have been discussing. An important difference is that this "search for the best evidence" invariably points to the so-called Cochran Reviews, a database of systematic reviews and meta-analyses which aims to make the results of well-conducted clinical trials readily available. Here "well-conducted" translates to randomized and controlled, and the "critical appraisal" amounts to checking that these conditions are satisfied in order to ensure we have indeed included only the "best evidence".

Literal, aggressive application of these ideas is fraught with difficulty as is well-documented in the literature. Indeed, the JECP is itself a major forum for such critiques. See, for example, Rosenfeld.[24] We have emphasized[24] that trial purpose will often dictate designs other than the RCT and that strict reliance on the RCT has distorted clinical practice.[13]

And, irrespective of trial design, the question remains: Are these results applicable to one's patient? Probabilities need to be conditioned to account for any salient features of the individual and the context in which they will be applied.

6.3 | Is more evidence needed?

> "*The trouble with the world is not that people know too little; it's that they know so many things that just aren't so*". ~ Mark Twain

The kind, amount, quality and reliability of the evidence required to produce actionable clinical knowledge in a given situation is a matter of judgement and one can expect honest differences of opinion. It is also clear that the evidence required depends on the situation. The risk/benefit ratio is of critical importance in clinical decision making and this ratio acquires meaning only when context is taken into account.

For example, Jonas Salk thought that the efficacy of his vaccine had already been established[25] and that a placebo-controlled trial was not required. This conclusion was challenged by advocates of the RCT and the final design was decided upon only after lengthy - and often heated - negotiation. This example also shows that the sufficient evidence question can have ethical as well as epistemological implications. Jonas Salk was adamant that the use of placebo in this case was unethical.

6.4 | Knowledge

> "*As a scientist, I don't believe anything. Science shouldn't use the word belief. There are things more likely and less likely. Science can say nothing with absolute certainty*". ~ Lawrence M. Krauss

> "*The key to good decision making is not knowledge. It is understanding. We are swimming in the former. We are desperately lacking in the latter*". ~ Malcolm Gladwell

These two opinions appear to reflect the difference between having no knowledge at all and having so much that we are "swimming in it". The problem is that setting the bar for knowledge at "absolute certainty" is that it is then so high that *nothing* can qualify as knowledge. The ideal of "absolute certainty" was put into perspective almost 50 years ago by Bronowski[26] who noted:

> "*One aim of the physical sciences has been to give an exact picture of the material world. One achievement of physics in the twentieth century has been to prove that that aim is unattainable*". ... "*All information is imperfect. We have to treat it with humility. That is the human condition; and that is what quantum physics says*" (353).

This recognition is often packaged in terms of Heisenberg's Uncertainty Principle, (the idea that no events, not even atomic events, can be described with *absolute certainty*) and the postmodernists have argued that since one cannot have perfect knowledge all of the time, one cannot ever have any "real" knowledge. This conclusion, however, is made possible only by the admittedly poor choice of the word *uncertain* to describe the situation: "[W]e are not uncertain; our knowledge is merely confined within a certain tolerance. We should call it the *Principle of Tolerance*" (Bronowski[26(p365)]).

It is in this spirit that we suggest that the difference between Krauss and Gladwell is better seen as a difference in emphasis. Whereas Krauss focuses on uncertainties, Gladwell points to understanding as a way to reduce these. But we need not choose between these. It's not chaos vs, determinism, one or the other, but rather the realization that a more fertile ground for thought is to be found somewhere in-between these poles.[26]

The above remarks set the stage for the final section, where we arrive at our destination, "actionable clinical knowledge". The key point is that no knowledge is *absolute*, but at the same time, things can often be pinned down within certain tolerances, and our uncertainty can be quantified to at the least the extent that we are able to say that one proposition is more (less) uncertain than another. Often, this is accomplished through the comparison of the reliability of the processes used to produce the knowledge, but other factors may also impinge: background knowledge (assumptions), experience, relevance to the problem in hand, etc. In a word, *context*.

6.5 | Actionable clinical knowledge.

"*Medicine is a science of uncertainty and an art of probability*". ~ William Osler

This quote by Osler recognizes the balance that needs to be achieved between the reduction of uncertainty and its acceptance. Medical science seeks to reduce uncertainty; medical practice must face the remaining probabilistic structure of intervention.

These probabilities are not easy to specify and must be conditioned to account for context and individual differences. Clinical decision-making is based on risk/benefit ratios and these acquire meaning only when context is considered. One must select tools appropriate for the job in hand (horses for courses). Sometimes doing nothing might be appropriate. Since health care providers are to do no harm, they will often start out by asking "Will watchful waiting work?" In other situations, prompt action will be required Finding a balance between these two extreme situations is often required and constitutes the art of medical practice.

7 | CONCLUSIONS

Clinical decision-makers, whether in research or clinical practice contexts, ask questions and try to answer them. The hope is, of course, to "arrive at the truth of the matter", but errors can creep in at several points along the way.[27] Clinical research and practice are *human* activities and the species can never produce answers with *absolute certainty*.

Clinical decision-making is not infallible, and the steps we can take to minimize error are context dependent. Medical evidence, produced as it is by human effort, can never be perfect. We will be doing well by assuring that the evidence we use has been produced by a reliable process and is relevant to the question posed.

We conclude with a final quote from Haack[1]:

> Inquiry is difficult and demanding, and we very often go wrong. Sometime the problem is a failure of will; we don't really want to know badly enough to go to all the trouble of finding out, or we really don't want to know, and go to a lot of trouble not to find out. And even with the best will in the world, we often fail. Our senses, our imaginations, and our intellects are limited; we can't always see, or guess, or reason, well enough. (24-5)

CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

AUTHOR CONTRIBUTIONS

C.K. devised the project and designed the figures. C.K. and R.R. wrote the manuscript with input from A.M. All authors agreed on the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed.

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