Clinical Practice Guidelines:

Challenges and Opportunities for Advancing Genomic Medicine

SESSION II: Why Guidelines Matter for Genomic Testing

Examining Clinical Guidelines for the Adoption of Genomic Testing: A Workshop

National Academies of Sciences, Engineering, and Medicine

Roundtable on Genomics and Precision Health - October 29, 2024

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Expertise that advances patient care through education, innovation, and advocacy.

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Disclosures

- Conflicts of interest
  - Financial
    - Employed by the Association for Molecular Pathology (AMP)
    - No additional conflicts to disclose
  - Professional associations
    - Member and volunteer: AMP, Guidelines International Network (GIN)
    - Member: American Association of Bioanalysts, American Society for Clinical Pathology, Association for Pathology Informatics, American Society of Association Executives

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High level overview & genomic medicine considerations

Guideline development process / methodology overview

5 questions about practice guidelines

What's new, what's next

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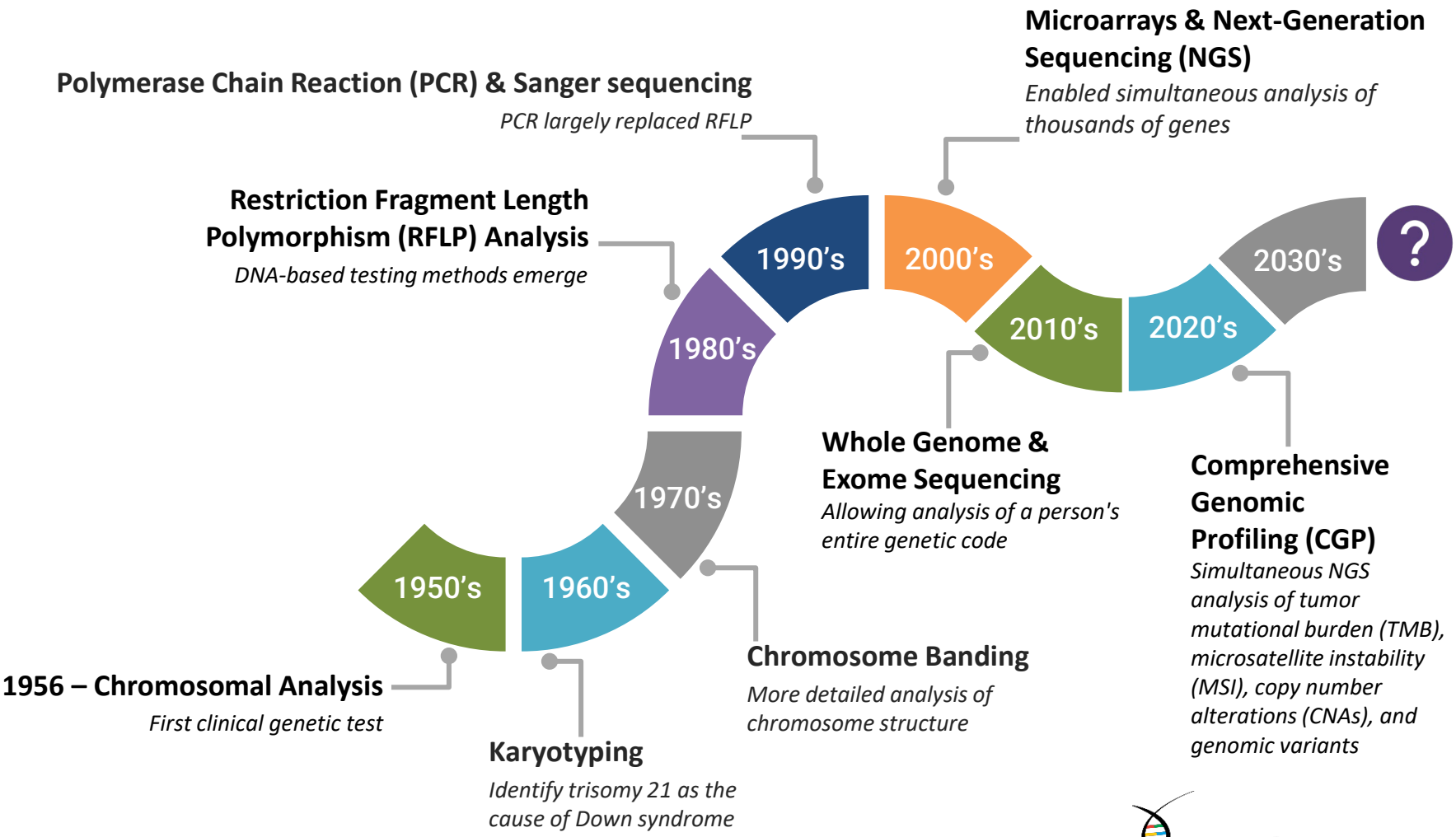
1956 -> 2024: 67 years of clinical genomic medicine



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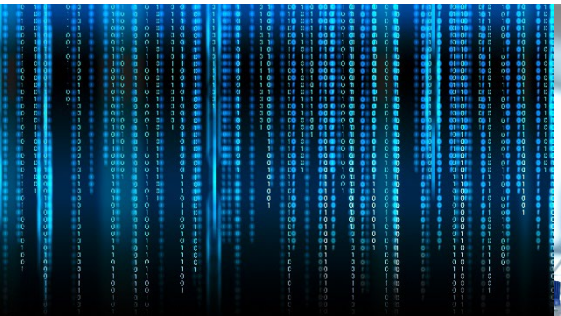
Guideline developers have a challenging landscape to navigate with genomic medicine

- Rapidly evolving, highly technical clinical practice area
- Sheer volume and complexity of genomic data
- Limited and/or emerging high-quality clinical evidence
- Limited integration into widescale routine clinical practice (currently)
- Diversity and equity concerns, ethical and social implications
- Used in many clinical areas (infectious disease, oncology, medical genetics, pharmacogenomics, transplant…)
- Rapidly changing technologies
- Diverse applications of same technology



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Defining a Clinical Practice Guideline (CPG)

- A document that focuses on a disease or condition and includes recommendations for appropriate management of patients with this disease or condition

What is the clinical question? What is the patient population? What is the desired outcome of the intervention?

- Should be based on the best available evidence and should help healthcare providers by supplementing their knowledge and skills

What evidence do we have? Do the studies measure the same outcomes? Is the evidence we have clinically relevant to this population?

- Can be tailored to clinical, health policy, health systems or public health settings, among others

Who is the end user? Who are the stakeholders? Do the proposed recommendations align with patient preferences and values?

Guidelines International Network (GIN)-McMaster Guideline Development Checklist Glossary of Terms
https://macgrade.mcmaster.ca/wp-content/uploads/2023/09/checklistglossaryprintable.pdf

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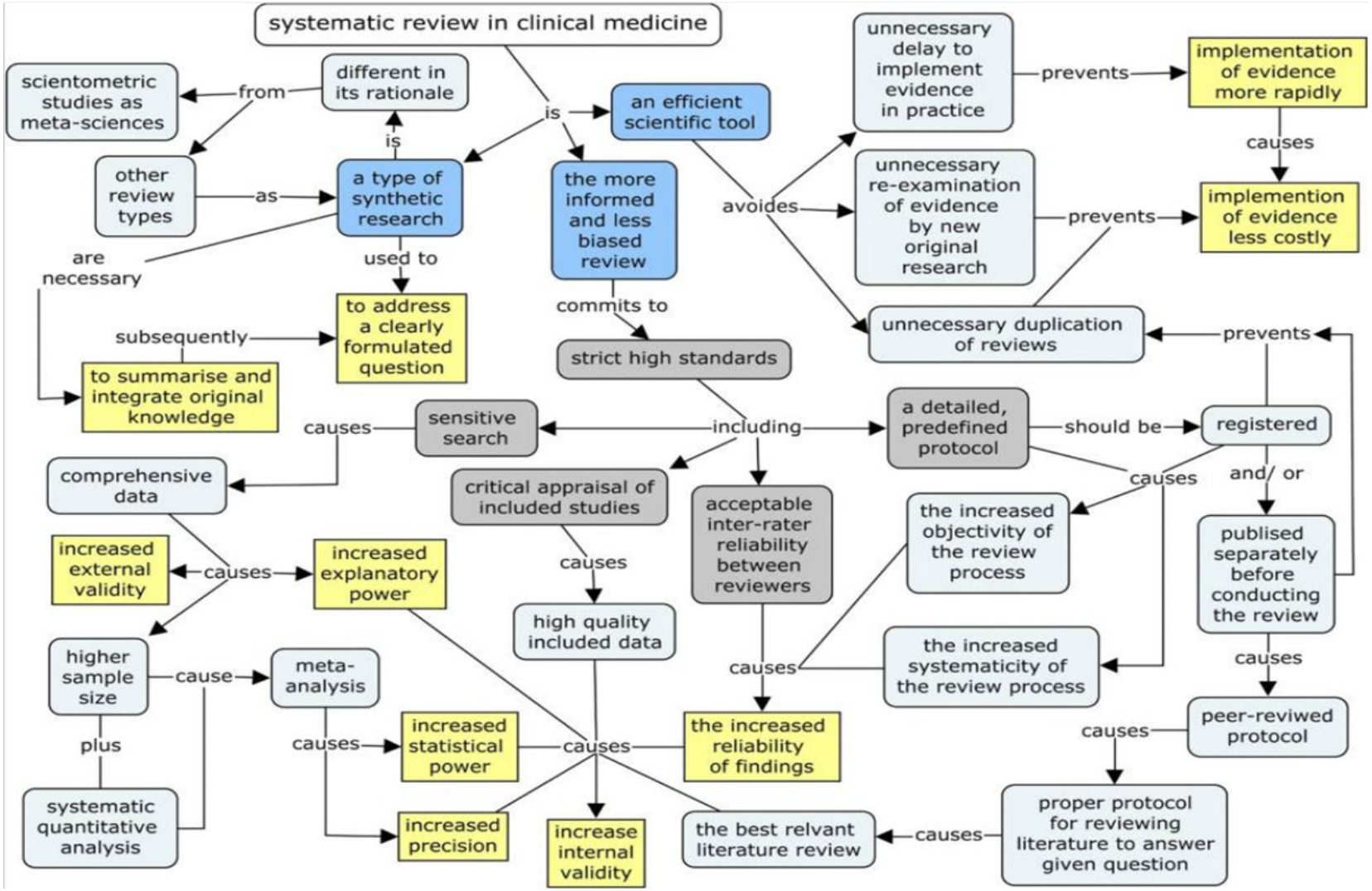
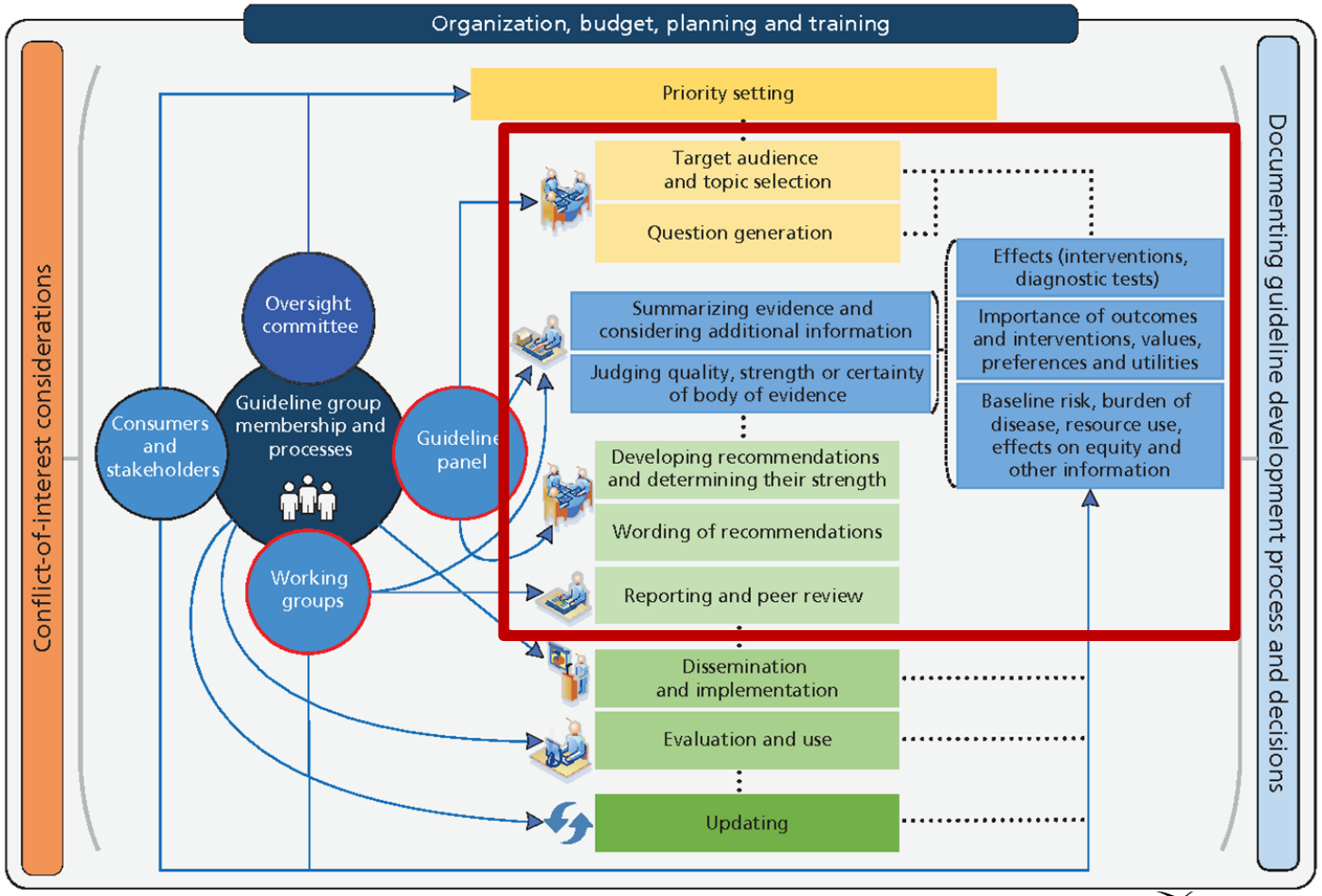
The Rationale behind Systematic Review in Clinical Medicine: a Conceptual Map



J Diabetes Metab Disord. 2021 Jun; 20(1): 919–929

Evidence-based CPG development process



CMAJ Feb 2014. 186 (3) E123-E142

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Important to understand PICO(s) & key questions

- Patient, Population or Problem
  - What are the characteristics of the patient or population (demographics, risk factors, pre-existing conditions, etc)? What is the condition or disease of interest?
- Intervention
  - What is the intervention under consideration for this patient or population?
- Comparison
  - What is the alternative to the intervention (e.g. placebo, different drug, surgery)?
- Outcome
  - What are the included outcomes (e.g. quality of life, change in clinical status, morbidity, adverse effects, complications)?

Specific who, what, when, where and how, of an EBHC research question

Guides literature review inclusion / exclusion criteria selection
Identifies specific data elements for extraction & subsequent analysis
to support recommendation statements

https://www.cochranelibrary.com/en/about-pico

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Traditional systematic review (SR) & meta-analysis process

Living systematic review (LSR) & meta-analysis process

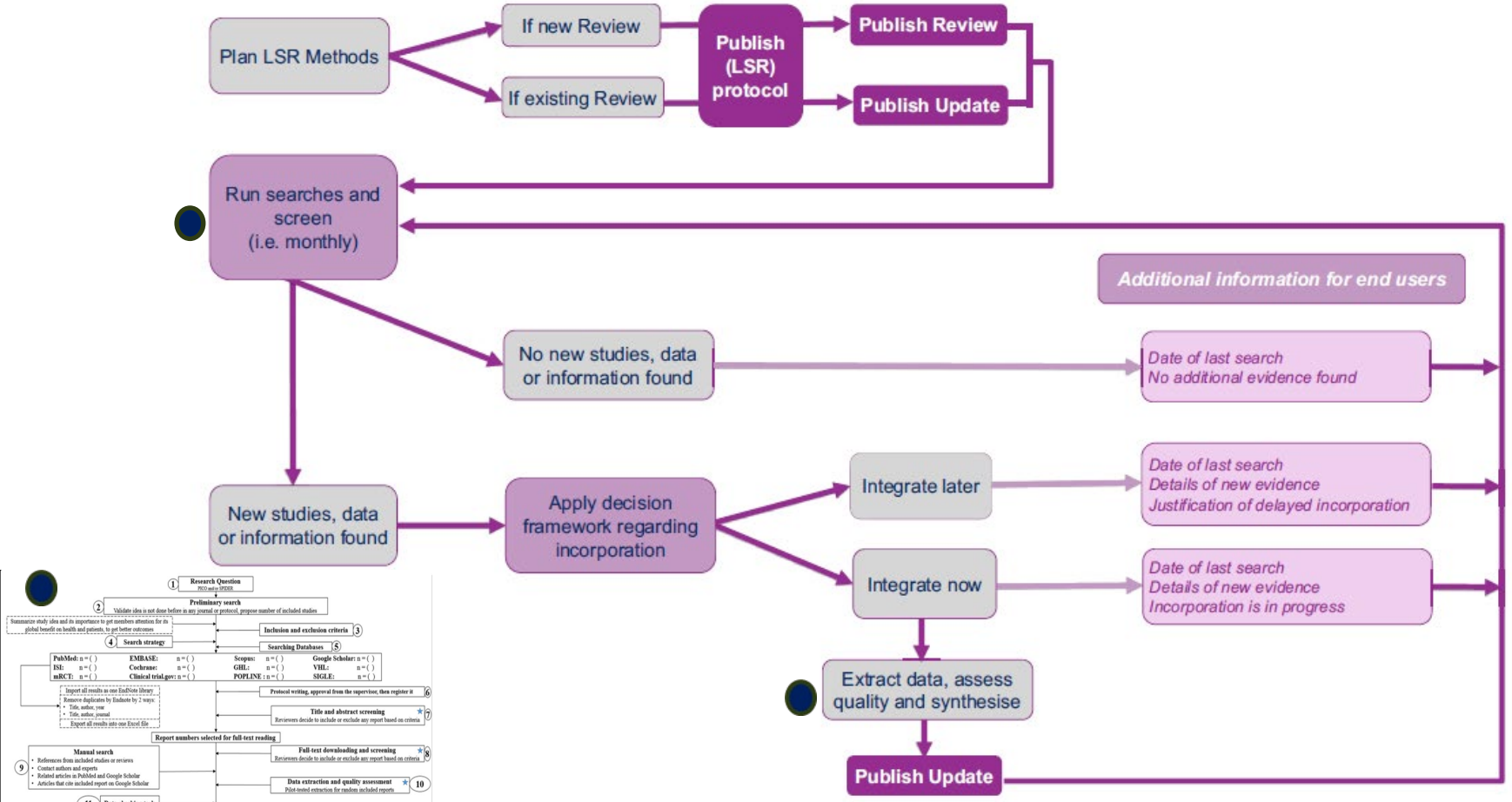

Fig. 1. Update scenarios. LSR, Living systematic review.

Fig. 1 Detailed flow diagram guideline for systematic review and meta-analysis steps. Note: Star icon refers to "2–3 reviewers screen independently"

[J Clin Epidemiol. 2017 Nov:91:23-30](#)

[Trop Med Health. 2019 Aug 1:47:46](#)

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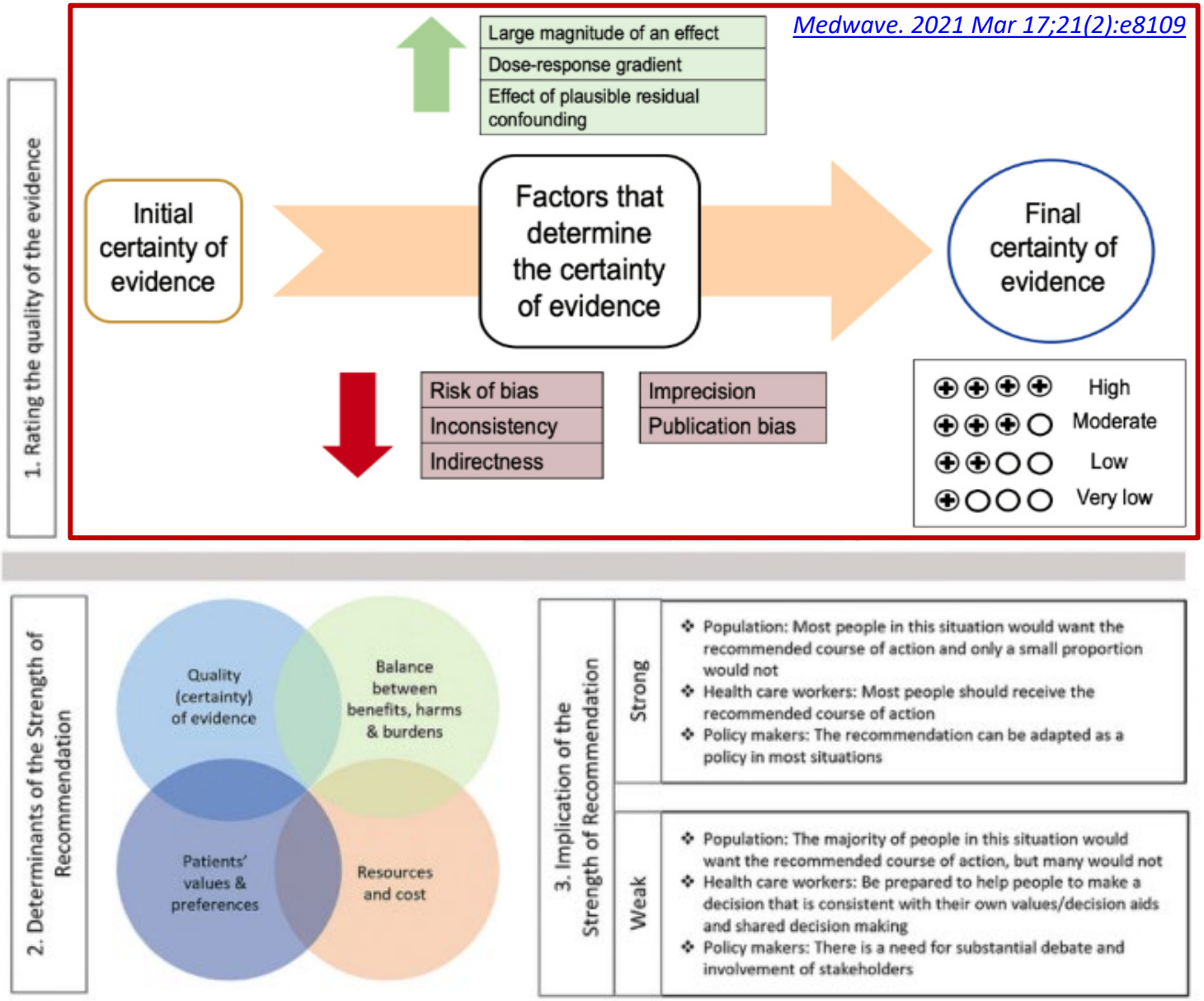

Medwave. 2021 Mar 17;21(2):e8109

Infect Dis Ther (2022) 11:2063–2098

GRADE summary of findings (SoF) table

Table 3. Example of an SoF table

AAP compared with no AAP for pregnant women with prior VTE*					
				Anticipated absolute effects	
Outcomes	**No. of participants (studies)**	**Certainty in the evidence (GRADE)†**	**Relative effect, RR (95% CI)‡**	**Risk with no AAP**	**Risk difference with AAP**
Recurrent major VTE (PE or proximal DVT)	1519 (11 observational studies)[53]§‖	⊕⊕◯◯ Low	0.39 (0.21-0.72)	42 per 1000	26 fewer per 1000 (33 fewer to 12 fewer)
Major bleeding, antepartum	943 (6 RCTs)[54]¶	⊕⊕◯◯ Low#	0.34 (0.04-3.21)	6 per 1000	4 fewer per 1000 (6 fewer to 14 more)
Major peripartum bleed	799 (8 RCTs)[54]¶	⊕⊕◯◯ Low#	0.82 (0.36-1.86)	30 per 1000	5 fewer per 1000 (19 fewer to 26 more)
Thrombocytopenia	945 (8 RCTs)[54]	⊕◯◯◯ Very low#**	2.37 (0.92-6.11)	13 per 1000	17 more per 1000 (1 fewer to 64 more)

Bates et al.[1] Click here for interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_01618857-BE05-A8CA-8C89-E76E69C5FDD3-1582467465073?_k=w7ov9s.

AAP, antepartum anticoagulant prophylaxis; RR, risk ratio; SoF, summary of findings.

*Patient or population: pregnant women with prior VTE. Setting: inpatient or outpatient setting. Intervention: antepartum anticoagulant prophylaxis. Comparison: no antepartum anticoagulant prophylaxis.

†GRADE Working Group grades of evidence: high certainty, we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty, we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low certainty, our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; very low certainty, we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

‡The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

§Total of 11 studies; 8 had a group that received antepartum prophylaxis; 9 had a group with no antepartum prophylaxis. Of the 11, 7 were retrospective, 4 were prospective (3 were randomized comparisons).

‖Provoked, unprovoked, or estrogen associated in LMWH.

¶Most women had a history of placenta-mediated pregnancy complications; none had a history of prior VTE.

#The very low event rate leads to uncertainty.

**Not a direct outcome of interest, which leads to uncertainty.

Blood Adv. 2020 May 12;4(9):2095-2110

Factors influencing strength of recommendations

Table 2. Criteria that influence the strength and direction in the GRADE EtD frameworks

Criteria	How the criterion influences the direction and strength of a recommendation
1. Problem	The judgment about the problem is determined by the importance and frequency of the health care issue that is addressed (burden of disease, prevalence, cost, or baseline risk). If the problem is of great importance an intervention is more likely to exert large effects and a strong recommendation may be more likely. However, this is a guiding principle and not universally applicable to all recommendations.
★ 2. Values and preferences or the importance of outcomes	This describes how important health outcomes are to those affected, how variable they are, and whether there is uncertainty about this.
3. Certainty in the evidence about the health benefits and harm	The higher the certainty in the evidence, the more likely is a strong recommendation.
4. Health benefits and harms and burden and their balance	This requires an evaluation of the absolute effects of both the benefits and harms and their importance including the judgment about criterion 2. The greater the net benefit or net harm, the more likely is a strong recommendation for or against the option.
★ 5. Resource implications	This describes how resource intense an option is, if it is cost-effective and if there is incremental benefit. The more advantageous or clearly disadvantageous these resource implications are, the more likely is a strong recommendation.
★ 6. Equity	The greater the likelihood to reduce inequities or increase equity and the more accessible an option is, the more likely is a strong recommendation.
7. Acceptability	The greater the acceptability of an option to all or most stakeholders, the more likely is a strong recommendation.
8. Feasibility	The greater the acceptability of an option to all or most stakeholders, the more likely is a strong recommendation.

★ *Healthcare equity, patient preferences and values, and resource implications are intentionally and proactively considered when developing CPG recommendations using GRADE Evidence to Decision frameworks*

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Crafting recommendation statements

- Should follow a structure & preferred language that clearly identifies
  - who the recommendation is for
  - what is recommended and against what alternative
  - the strength of the recommendation
  - the certainty in evidence that supports the intervention effects,
  - complementary guidance included as remarks,
  - who is making the recommendation

- Example 1: For pregnant women with proven acute superficial vein thrombosis, the ASH guideline panel suggests using LMWH over not using any anticoagulant (conditional recommendation based on low certainty in the evidence of effects ⊕⊕OO)

- Example 2: For pregnant women with acute VTE, the ASH guideline panel recommends antithrombotic therapy compared with no antithrombotic therapy (strong recommendation based on high certainty in the evidence about effects ⊕⊕⊕⊕)

Blood Adv. 2020 May 12;4(9):2095-2110

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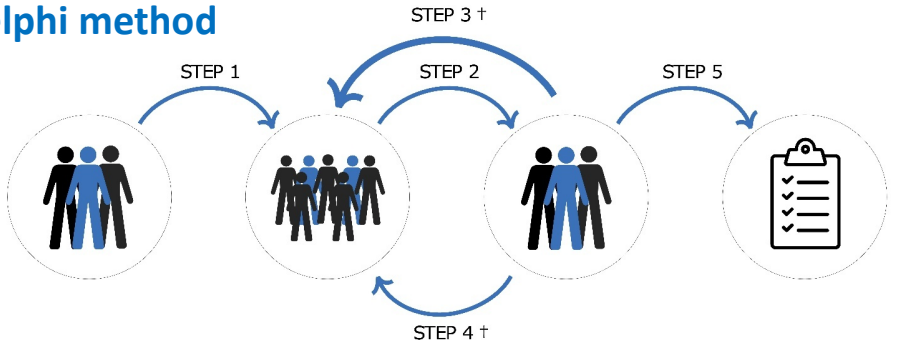
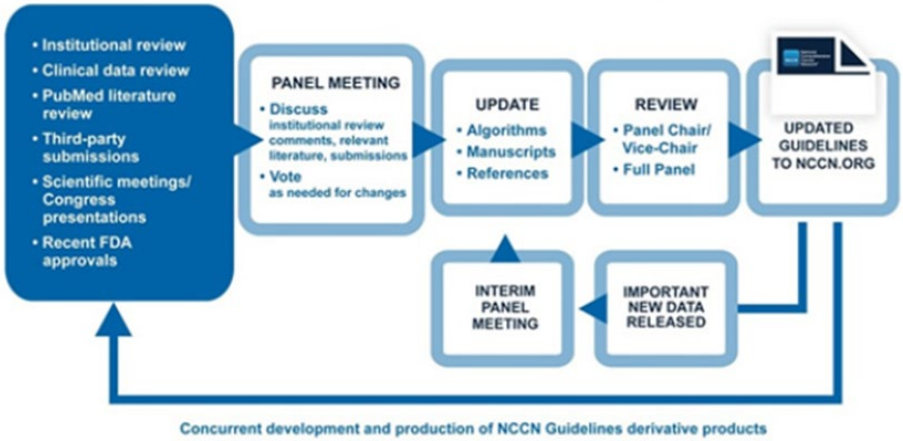
Evidence-based consensus recommendation development CPG processes that are not GRADE

Delphi method



† Steps 3 and 4 can be repeated additional times as per the study

Panel discussion & voting method



RAND/UCLA modified Delphi panel method

J Healthcare Leadership 2022:14 63–70; AJOPS. 2024;7(1);
https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines

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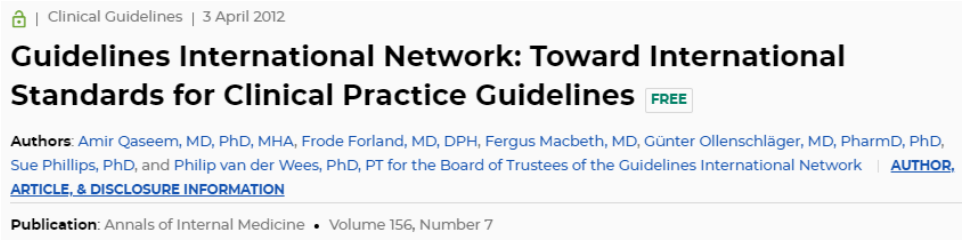
GIN Key Components of Trustworthy Guidelines

- **Composition of guideline development group:** Should include diverse stakeholders like health professionals, methodologists, topic experts, and patients
- **Transparent decision-making process:** The process for reaching consensus should be described
- **Conflicts of interest:** Financial and non-financial conflicts of interest should be disclosed and managed
- **Clear scope and objectives:** The guideline should specify its aims and scope
- **Rigorous development methods:** The methods used should be clearly described in detail


Clinical Guidelines | 3 April 2012

Guidelines International Network: Toward International Standards for Clinical Practice Guidelines FREE

Authors: Amir Qaseem, MD, PhD, MHA, Frode Forland, MD, DPH, Fergus Macbeth, MD, Günter Ollenschläger, MD, PharmD, PhD, Sue Phillips, PhD, and Philip van der Wees, PhD, PT for the Board of Trustees of the Guidelines International Network | AUTHOR, ARTICLE, & DISCLOSURE INFORMATION

Publication: Annals of Internal Medicine • Volume 156, Number 7

- **Systematic evidence reviews:** Systematic methods should be used to identify and evaluate evidence
- **Evidence-based recommendations:** Recommendations should be based on scientific evidence of benefits, harms, and costs
- **Rating of evidence and recommendations:** A rating system should communicate the quality of evidence and strength of recommendations
- **External review:** Review by external stakeholders should occur before publication
- **Updating process:** An expiration date or updating process should be included
- **Funding transparency:** Financial support for development should be disclosed

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1. What groups are involved in CPG development and how/when do they participate?

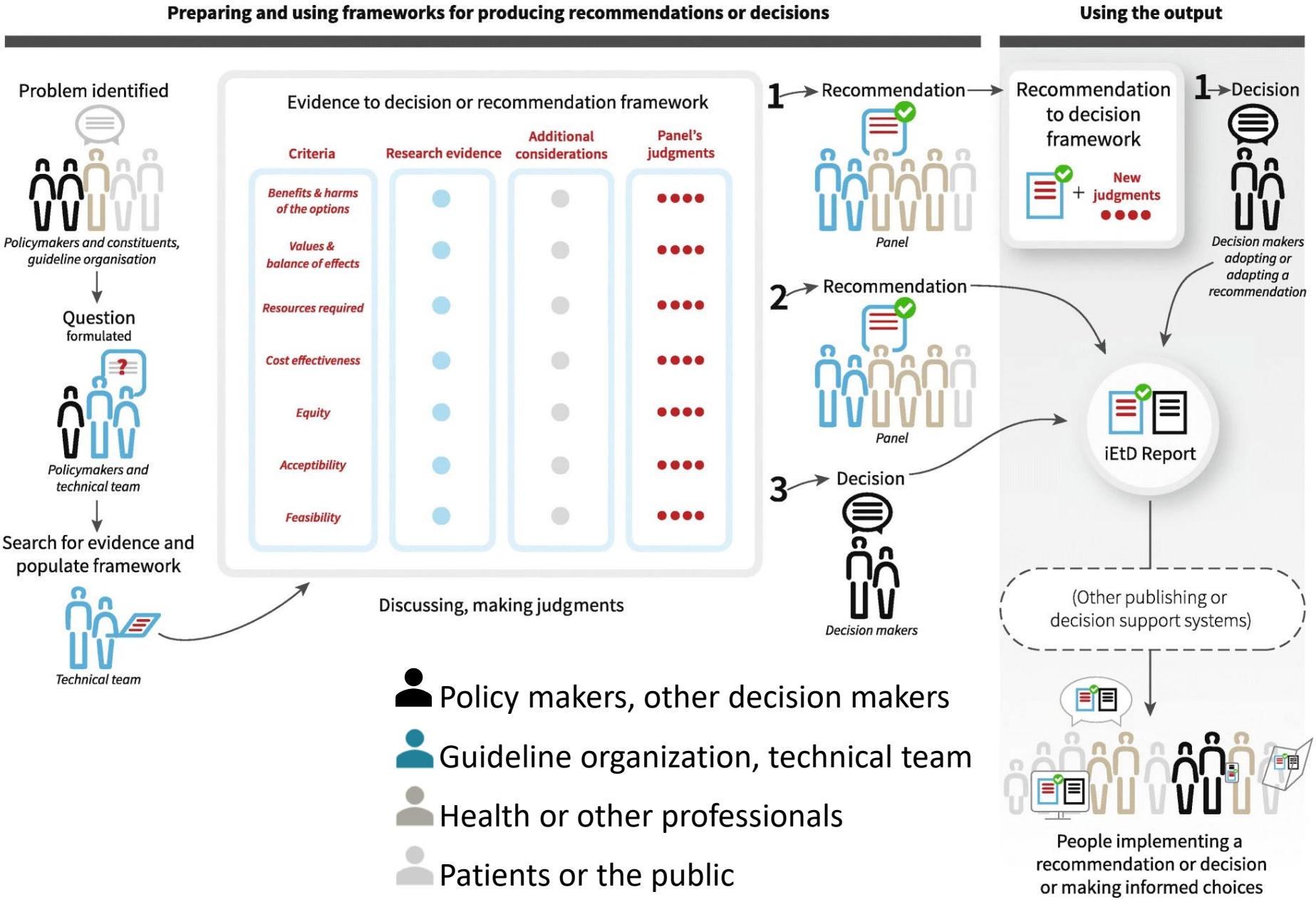
2. What is the difference between CPGs, clinical consensus statements, and position statements?

3. How can CPGs on the same topic and evaluating the same literature make different recommendations?

4. Why don't you make every CPG an LCPG?

5. Does a strong recommendation apply to every patient?

BONUS QUESTIONS: Why could the process be slower than ideal even with living guidelines, lots of SR technology, AI/ML?



Health Research Policy and Systems 2018. 16:45

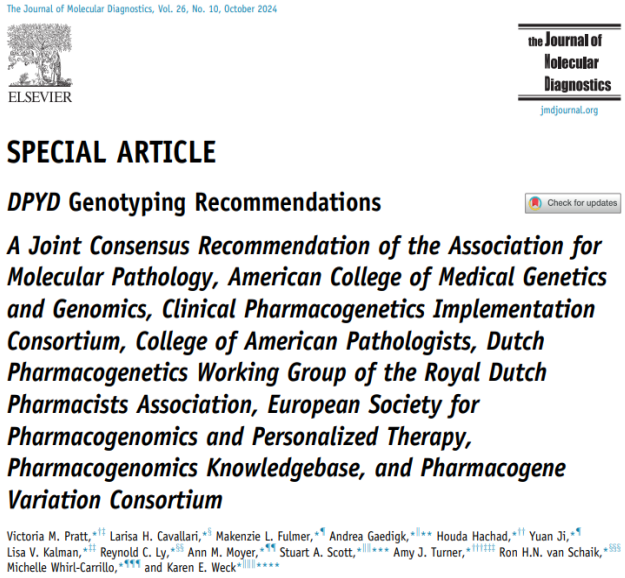
What is the difference?

European Academy of Neurology *Eur J Neurol. 2021; 28:2461–2466 Table 2 modified*	CPGs	Clinical consensus statements	Position paper
Scope	Broad	Usually narrow	Narrow
Multidisciplinary panel	✓	If necessary	If necessary
Clinical question generation (PICO tool)	✓	Desirable	If necessary
Outcome importance voting (GRADE method)	✓	✗	✗
Systematic review for each PICO	✓	Desirable	✗
Grading the quality of the studies (multiple methods)	✓	Desirable	✗
Rates strength of evidence for each outcome and overall (GRADE method)	✓	✗	✗
Determines direction & strength of a recommendation (GRADE method)	✓	✗	✗
Reaching consensus with formal methods	If necessary	If necessary	Desirable


All are tools in a very large toolbox
Match the tool to the project

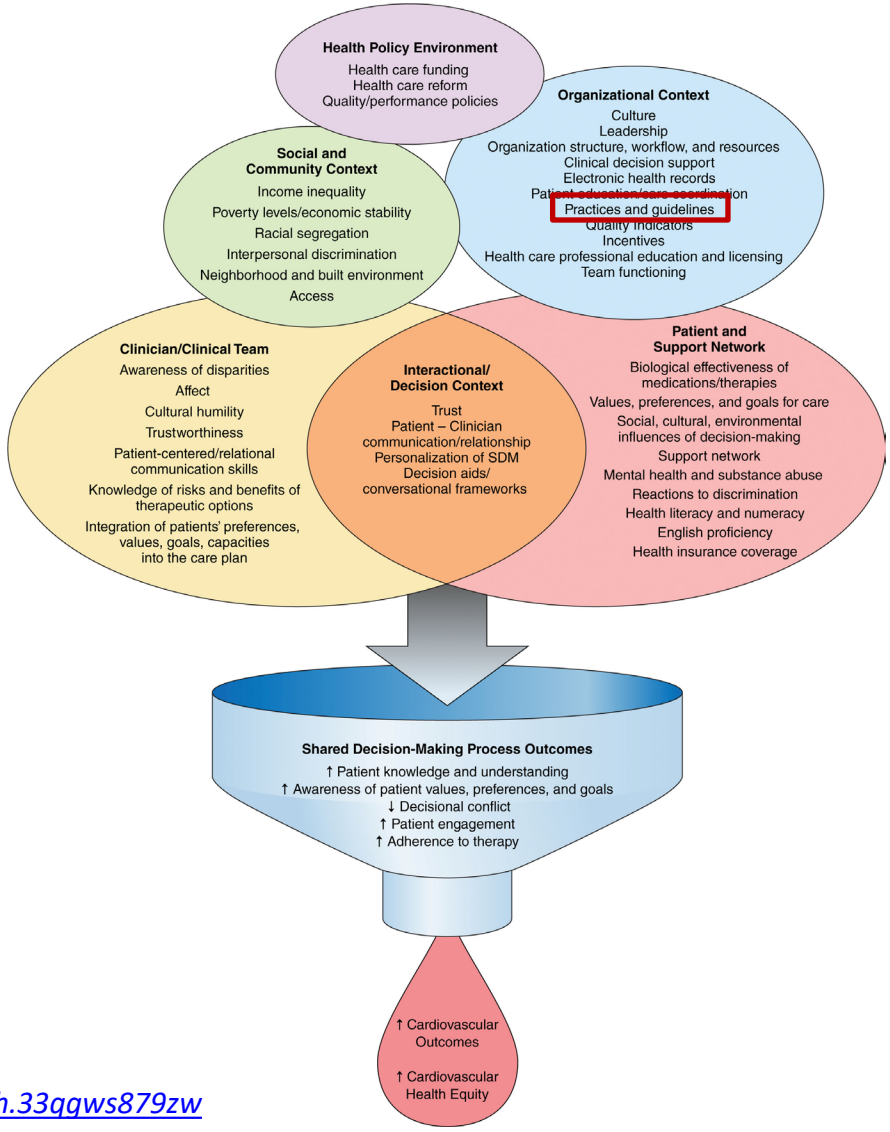
Expert clinical practice statements / clinical consensus statements play an important role

- Recommendations or guidance are needed AND there is uncertainty on the best course of action
  - Clinicians need to make decisions *for current patients*
  - Identified need to establish best practices for patient care *now*
  - Literature is emergent, inconsistent, or limited *at this point in time*
- Frequently occurs in rapidly evolving fields
- Evidence-based, use established consensus methods informed by relevant professional expertise and experience



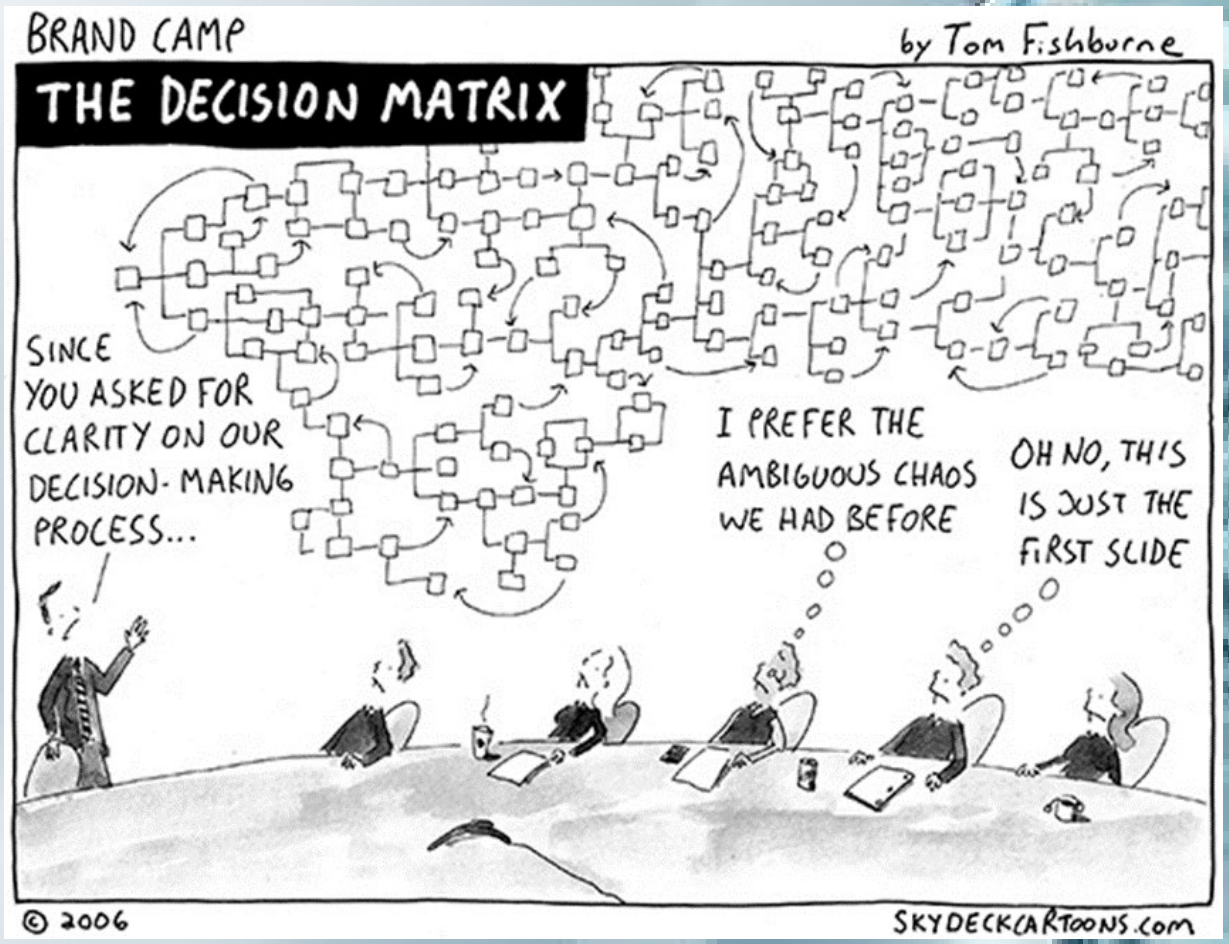
CPG recommendations are NOT dictates

- Even strong recommendations based on high-quality evidence will not apply to all circumstances and all patients
  - Following some strong recommendations based on high-quality evidence will be a mistake for some patients
  - No CPG or recommendation can account for all the often-compelling unique features of individual patients and clinical circumstances
  - End users should not attempt to apply recommendations by rote or in a blanket fashion
- Clinical decision support tools
- Support shared decision-making processes



Circulation. 2023 Sep 12;148(11):912-931;
GRADE Handbook: https://gdt.gradepro.org/app/handbook/handbook.html#h.33qgws879zw

Question #3: How can CPGs on the same topic and evaluating the same literature make different recommendations?



Many potential causes of CPG differences

Methodology / standards

GRADE or expert consensus

Traditional or living format

Scope and focus

Broad or narrow

End users are primary care or specialists

PICO elements

Different patient populations, outcomes, interventions, comparators considered / prioritized

Target audience

May emphasize different aspects of care for specific groups

Evidence interpretation

May interpret differently based on expertise & perspective

Patient representation

Panel representation & level of engagement can influence recommendations

Values & preferences

Different ones considered / emphasized in formulating recommendations

Resource considerations

Some factor in cost & resource use more heavily than others

Stakeholder involvement

Targets & level of engagement can influence recommendations

Updating frequency

Developed / updated at different times may have access to different evidence

Conflict of interest management

Varying approaches can impact final content

Cultural / geographic context

May account for variability in practices, resources, & epidemiology

Organizational mission

Mission & priorities can shape focus & recommendations

Collaboration level

Single or multiorganizational development

Intended CPG use

Diagnosis, intervention, diagnostic test, prognosis, policy

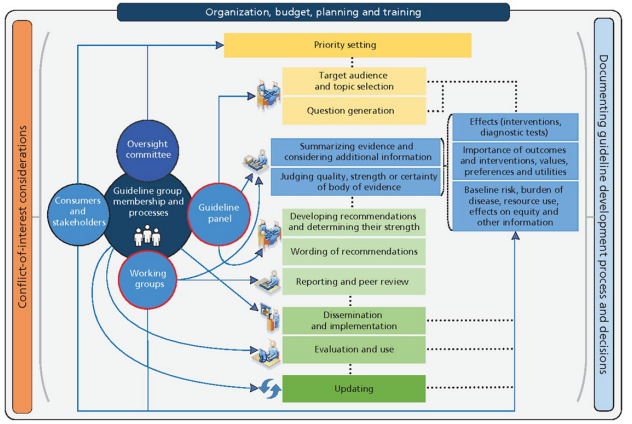
Development process rigor

More rigorous may lead to different conclusions than less formal

Living guidelines update faster, but pose new development challenges

Table 3. Key differences between traditional and living guidelines

Key element	Traditional guideline	Living guideline
Governance structures and team	Usually for a fixed term.	Ongoing, responsive, adaptive, and allowing for turnover.
Conflicts of interest	Declared throughout the fixed term of the project.	Declared continually over the ongoing project and adjudicated for relevance at the level of the individual recommendation.
Guideline scope	Established at the start and does not change.	May be revised throughout the development process.
Prioritization of clinical questions	Questions are prioritized for completion in the fixed period of the project.	Questions can be prioritized for varying intensities of living mode and priorities may be revised throughout the process, with opportunities to add new questions.
Engagement of clinical experts, decision-makers, leadership, and evidence team	For the fixed period of the project.	Ongoing. Needs a team culture that enables adaptive, dynamic, and responsive work.
Consumer involvement	For the fixed period of the project.	Ongoing engagement that allows for turnover and can evaluated and improved over time.
Guideline panel meetings	Regularly, for the fixed period of the project.	Ongoing, with inbuilt structures for member turnover.
Evidence surveillance and searching	At a prespecified timepoint during development and typically not repeated before publication.	Continual and may be conducted at different frequencies for each recommendation (e.g., weekly or monthly). The working group agreed that searches should be done at least once every 3 months to still be considered living.
Supportive information technologies and automation	Information technologies can support conducting evidence reviews (e.g., screening, data extraction, risk of bias, analysis, GRADE assessment) and publication.	Information technologies can enable living guidelines. Use of machine learning to automate processes.
Incorporating new evidence	Once, at the time of evidence review according to inclusion/exclusion criteria.	Continual, according to decision thresholds for when to incorporate new evidence.
Effect estimates, summaries of evidence, evidence profiles and certainty of evidence	Once, at the time of evidence review and recommendation development.	Continually updated and revised as new evidence is incorporated. The frequency is determined by the priority level of the recommendation.
Approval and endorsement	Once, at the end of the guideline development or updating.	At multiple timepoints, coordinated with external approval timelines and processes (e.g., from commissioning bodies). Approval for individual recommendations are usually sought, rather than for the entire guideline.
Public consultation on draft recommendations	Once, at the end of the guideline development or updating.	At multiple timepoints usually related to individual recommendations.
Publication and dissemination	Once, after completion of guideline development or updating.	Ongoing, at multiple timepoints, as new recommendations are generated, or changes are made to individual recommendations.



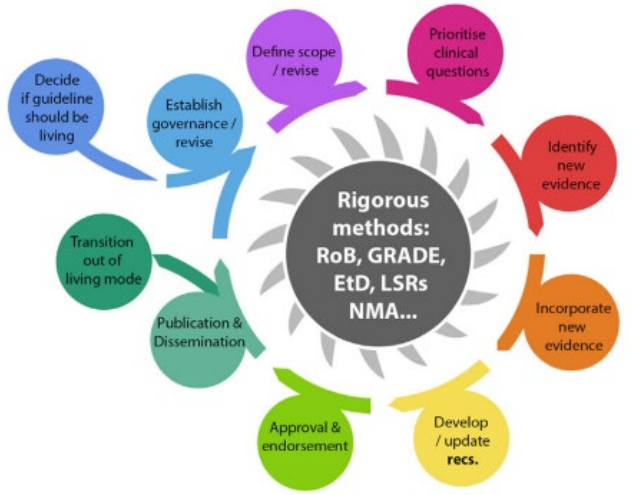


Fig. 1. Development cycle of a living guideline.

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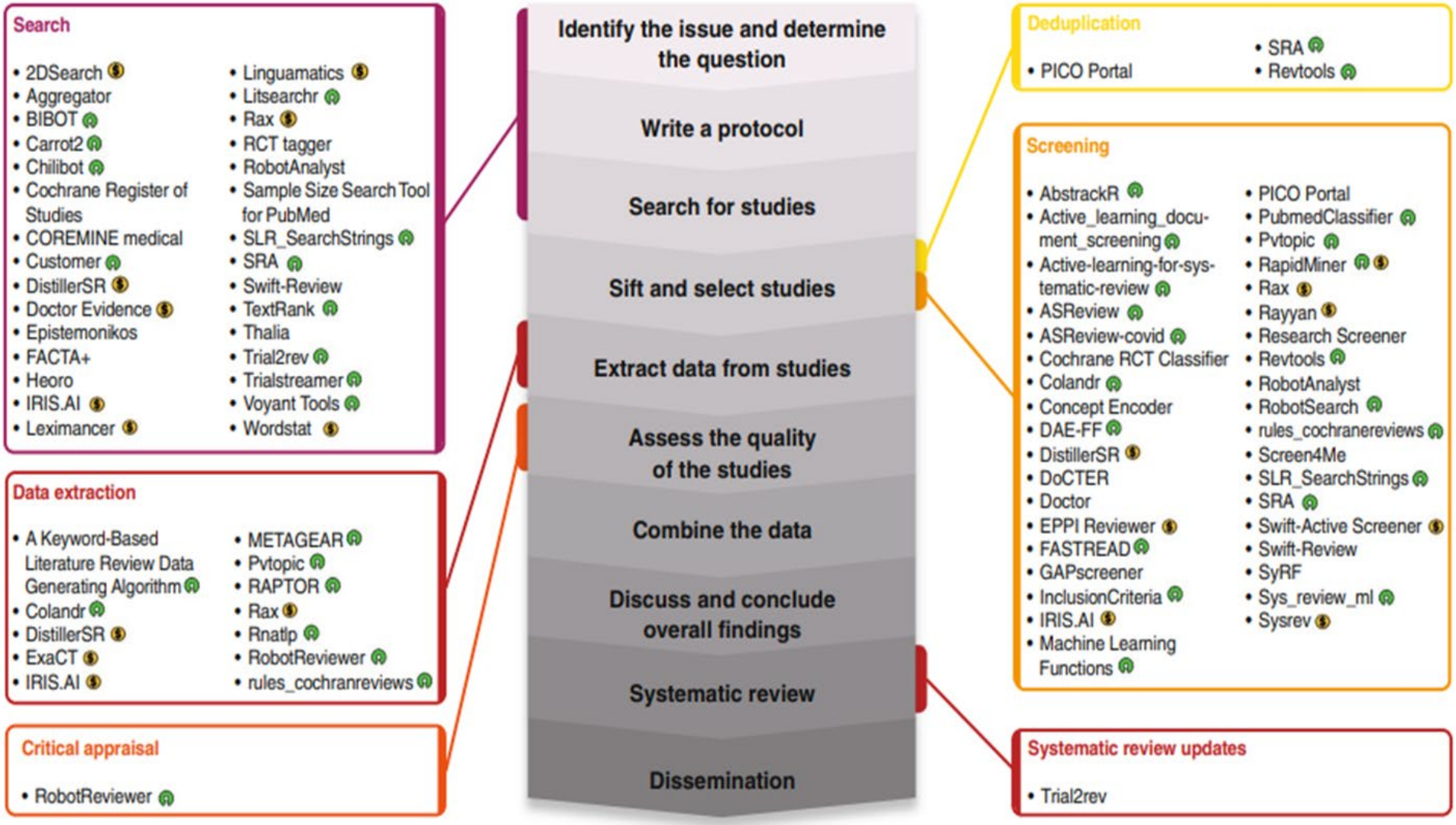
AI/ML Software tools to assist the SR process

BMC Med Res Methodol. 2022 Dec 16;22(1):322



Multiple reasons for long development times

medRxiv preprint Bastarache et al, 2024
doi: https://doi.org/10.1101/2024.10.17.24315685

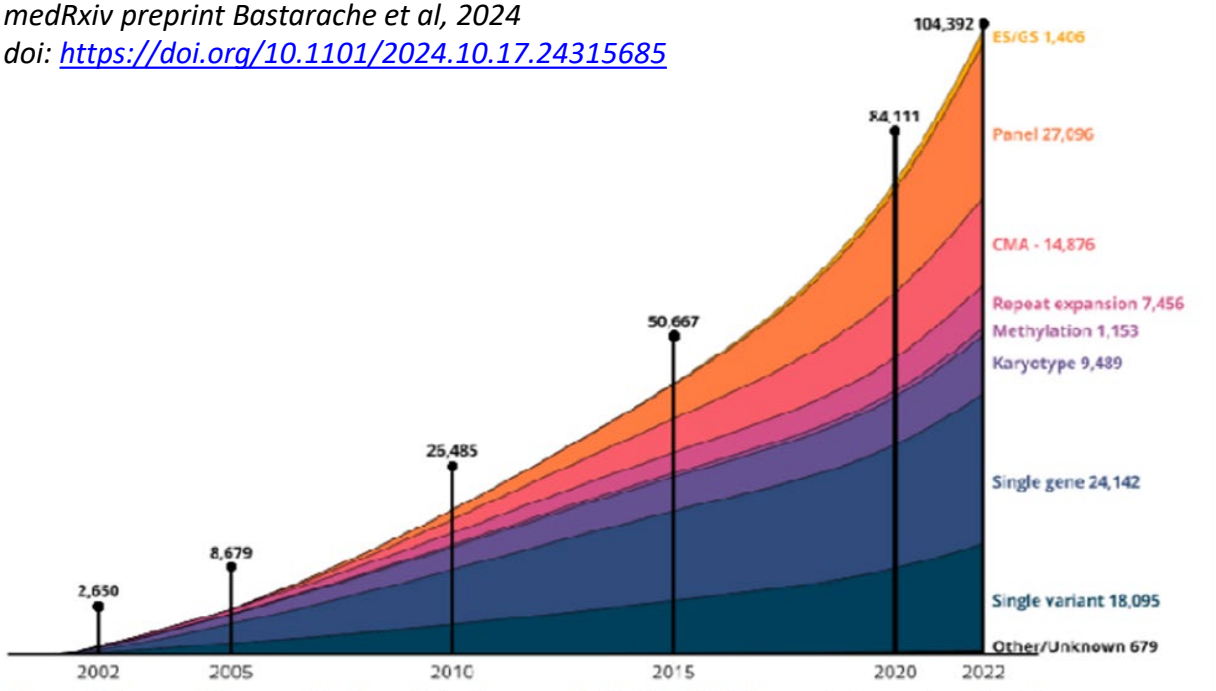
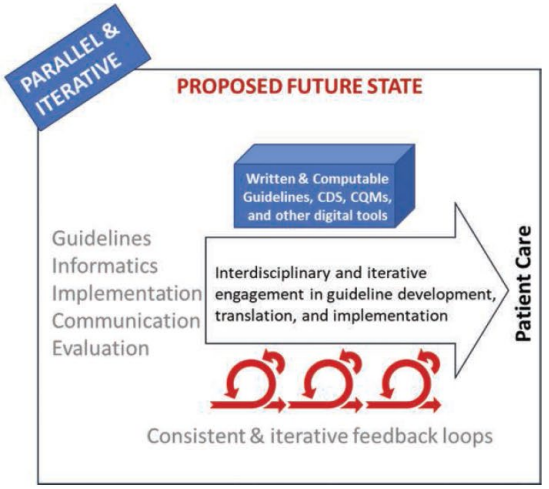


***Figure 1.* The cumulative growth of genetic testing recorded in the EHR.** The cumulative number of tests by year, stratified by test type. Cumulative counts of tests are shown at years 2002, 2005, 2010, 2015, and 2022, and cumulative totals for each test type are labeled on the right side of the figure.



l Qual. 2023 Sep-Oct;38(5S Suppl 2):S3-S11

will aid evidence synthesis, but other e more challenging & less malleable

al evidence ecosystem for improved health decision-making" discussions & investments could spark significant change (JBI/Cochrane/Campbell, Wellcome Trust, WHO)

- Complexity of topics
- Conflict resolution
- Implementation considerations

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CPG development employs various standardized methods using validated tools…

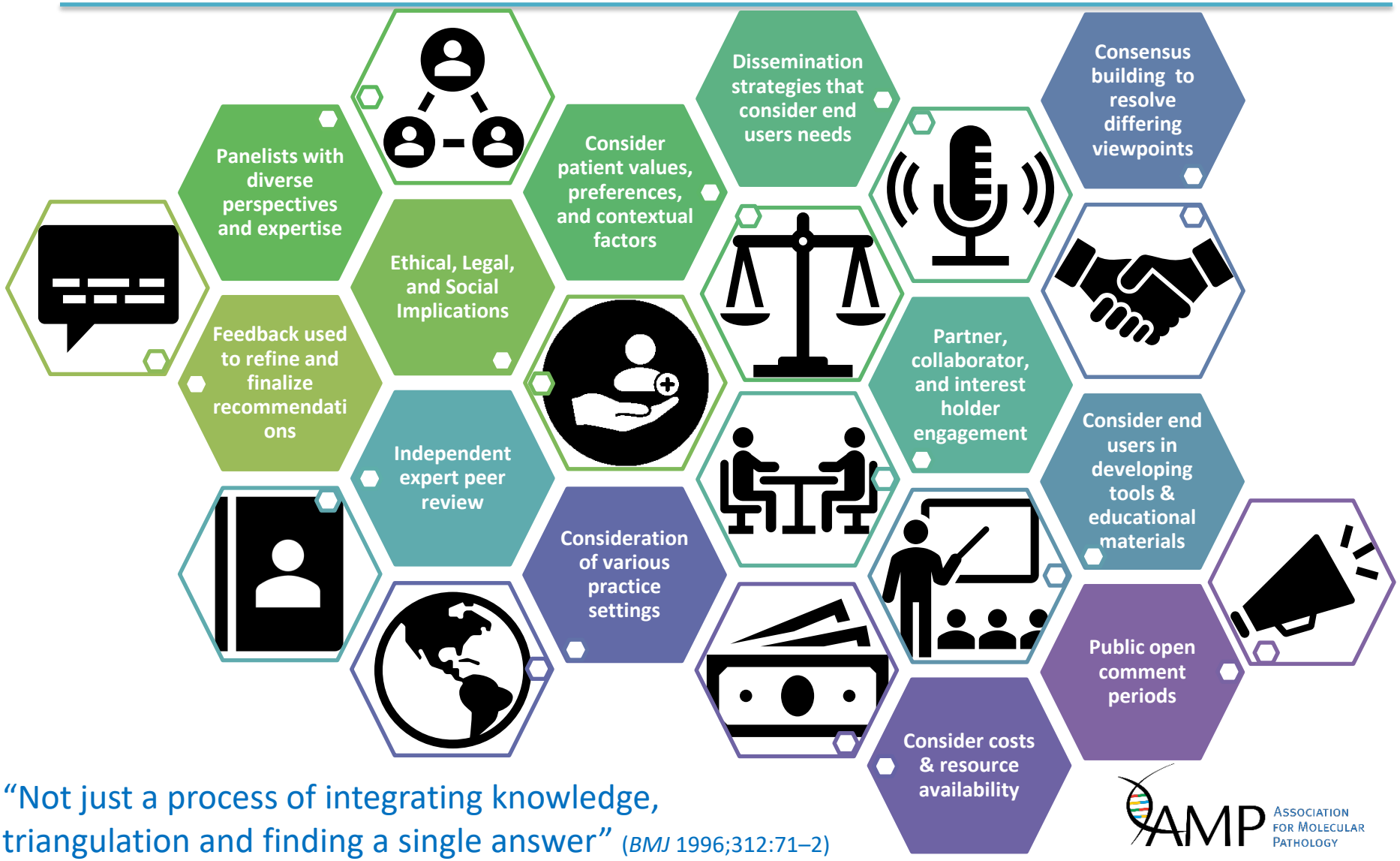
Table 6.3: Concise guide to best practices for evidence syntheses, version 1.0[a]

Resources	Intervention	Diagnostic	Prognostic	Qualitative or mixed methods	Prevalence and incidence	Etiology and risk	Measurement properties	Overviews (umbrella reviews)	Scoping reviews
Methodological guidance	Cochrane[b], JBI	Cochrane, JBI	Cochrane	Cochrane, JBI	JBI	JBI	JBI	Cochrane, JBI	JBI
Reporting[c] Protocol	PRISMA-P[116]	PRISMA-P	PRISMA-P	PRISMA-P	PRISMA-P	PRISMA-P	PRISMA-P	PRISMA-P	PRISMA-P
Systematic review	PRISMA 2020[112]	PRISMA-DTA[120]	PRISMA 2020	eMERGe[213,d] ENTREQ[214,d]	PRISMA 2020	PRISMA 2020	PRISMA 2020	PRIOR[215]	PRISMA-ScR[121]
Synthesis without meta-analysis	SWiM[180]		SWiM[e]		SWiM[e]	SWiM[e]	SWiM[e]		
RoB assessment of included studies[f]	For RCTs: Cochrane RoB2[157] For NRSI: ROBINS-I[158] Other primary research[g]	QUADAS-2[216]	Factor review QUIPS[217] Model review PROBAST[65]	CASP qualitative checklist[218] JBI critical appraisal checklist[219,h]	JBI checklist for studies reporting prevalence data[220]	For NRSI: ROBINS-I[158] Other primary research[g]	COSMIN RoB Checklist[67]	AMSTAR-2[6] or ROBIS[4]	Not required[i]
Overall level of evidence certainty	GRADE[27]	GRADE adaptation[j]	GRADE adaptation[k]	CERQual[221] ConQual[222,l]	GRADE adaptation[m]	Risk factors[n]	GRADE adaptation[o]	GRADE (for intervention reviews) Risk factors[n]	Not applicable

AMSTAR, A MeaSurement Tool to Assess Systematic Reviews; CASP, Critical Appraisal Skills Programme; CERQual, Confidence in the Evidence from Reviews of Qualitative research; ConQual, Establishing Confidence in the output of Qualitative research synthesis; COSMIN, COnsensus-based Standards for the selection of health Measurement Instruments; DTA, diagnostic test accuracy; eMERGe, meta-ethnography reporting guidance; ENTREQ, enhancing transparency in reporting the synthesis of qualitative research; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NRSI, non-randomized studies of interventions; P, protocol; PRIOR, Preferred Reporting Items for Overviews of Reviews; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROBAST, Prediction model Risk Of Bias ASsessment Tool; QUADAS, quality assessment of studies of diagnostic accuracy included in systematic reviews; QUIPS, Quality In Prognosis Studies; RCT, randomized controlled trial; RoB, risk of bias; ROBINS-I, Risk Of Bias In Non-randomised Studies of Interventions; ROBIS, Risk of Bias in Systematic Reviews; ScR, scoping review; SWiM, systematic review without meta-analysis.

JBI Evid Synth. 2023 Sep 1;21(9):1699-1731

…but it is also a human, social process

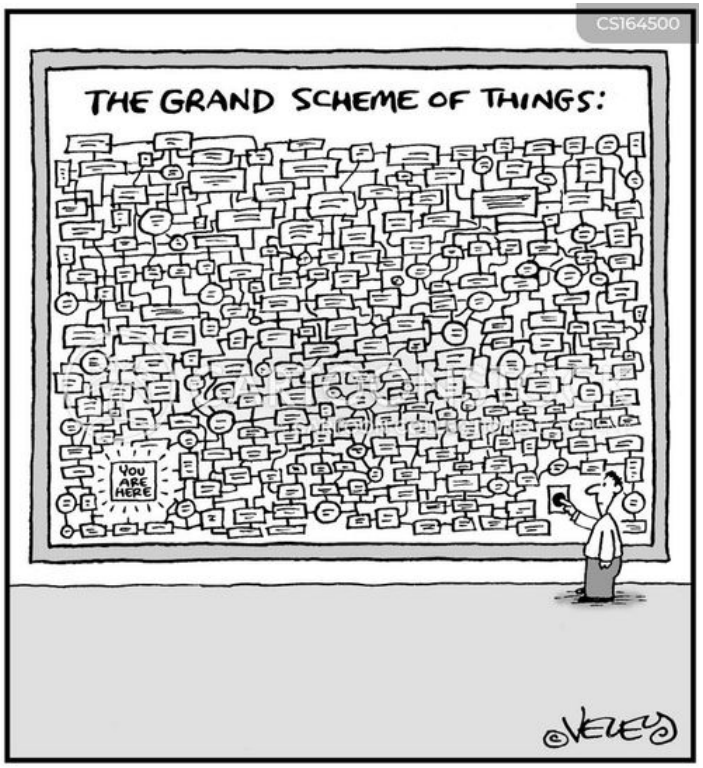


"Not just a process of integrating knowledge, triangulation and finding a single answer" (*BMJ* 1996;312:71–2)

AMP Association for Molecular Pathology

Clinical Practice Guidelines:

Challenges and Opportunities for Advancing Genomic Medicine



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