

The Role of Shared Decision Making in Navigating the Complex Treatment Landscape of R/R AML



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Reevaluating Genomic Mutations in R/R AML

Why is Reevaluation of Genomic Mutations Important in R/R AML?

Clonal evolution of AML can lead to the emergence and/or disappearance of actionable mutations at any timepoint in AML, including upon disease relapse¹

Mutational analysis allows:

-  Risk stratification (favorable, intermediate, and adverse risk groups)²
-  Prediction of remission rates, relapse risks, and OS outcomes (e.g. co-mutation of *FLT3*-ITD with *NPM1* showed higher survival probability than *FLT3*-ITD mutation alone)³
-  Monitoring of measurable residual disease (MRD)⁴
-  Targeted therapy selection, guided by mutations and risk stratification

Abbreviation: AML, acute myeloid leukemia; NPM1, nucleophosmin; FLT3-ITD, fms-like tyrosine kinase 3- internal tandem duplication; OS, overall survival

1. Morita K, et al. *Nature Communications*. 2020; 11:53272. 2. Döhner H, et al. *Blood*. 2022;140(12):1345-1377. 3. Papaemmanuil E, et al. *N Engl J Med*. 2016;374(23):2209-2221. 4. Jongen-Lavrencic M, et al. *N Engl J Med*. 2018;378(13):1189-99.

Actionable mutations in AML

Genes with actionable mutations	Prevalence*	Risk category ^{†12}
<i>NPM1</i>	28-35% ^{1,2}	Favorable and intermediate
<i>FLT3</i>-TKD	7-12% ^{3,4}	Intermediate
<i>FLT3</i>-ITD	21-32% ^{1,4}	
<i>IDH1</i>	8-14% ^{3,5}	Intermediate
<i>IDH2</i>	7-18% ^{3,5}	
<i>RUNX1</i>	5-10% ^{3,6}	Adverse
<i>CEBPA</i>	9-18% ^{3,7}	Favorable
<i>DNMT3A</i>	12-23% ^{3,8}	Intermediate
<i>KIT</i>	6-30% ^{3,9}	Intermediate
<i>ASXL</i>	3-11% ^{3,10}	Adverse
<i>TP53</i>	2-13% ^{3,11}	Adverse
<i>KMT2A</i>	—	Intermediate and adverse
<i>BCR:ABL</i> rearrangements	—	Adverse

* Approximate; observed prevalence varies among studies; † Risk category may depend on cytogenetics and co-mutations.

Abbreviations: AML, acute myeloid leukemia

1. Thiede C, et al. *Blood*. 2006;107(10):4011-4020. 2. Falini B, et al. *N Engl J Med*. 2005;352(3):254-266. 3. Patel JP, et al. *N Engl J Med*. 2012;366(12):1079-1089. 4. Schlenk RF, et al. *N Engl J Med*. 2008;358(18):1909-1918. 5. Messina M, et al. *Cancers*. 2022; 14:3012 6. Gaidzik VI et al. *Leukemia*. 2016;30(11):2160-2168. 7. Bienz M, et al. *Clin Cancer Res*. 2005;11(4):1416-1424. 8. Shen Y, et al. *Blood*. 2011;118(20):5593-5603. 9. Paschka P, et al. *J Clin Oncol*. 2006;24(24):3904-3911. 10. Chou WC, et al. *Blood*. 2010;116(20):4086-4094. 11. Papaemmanuil E, et al. *N Engl J Med*. 2016;374(23):2209-2221. 12. Döhner H, et al. *Blood*. 2022;140(12):1345-1377.

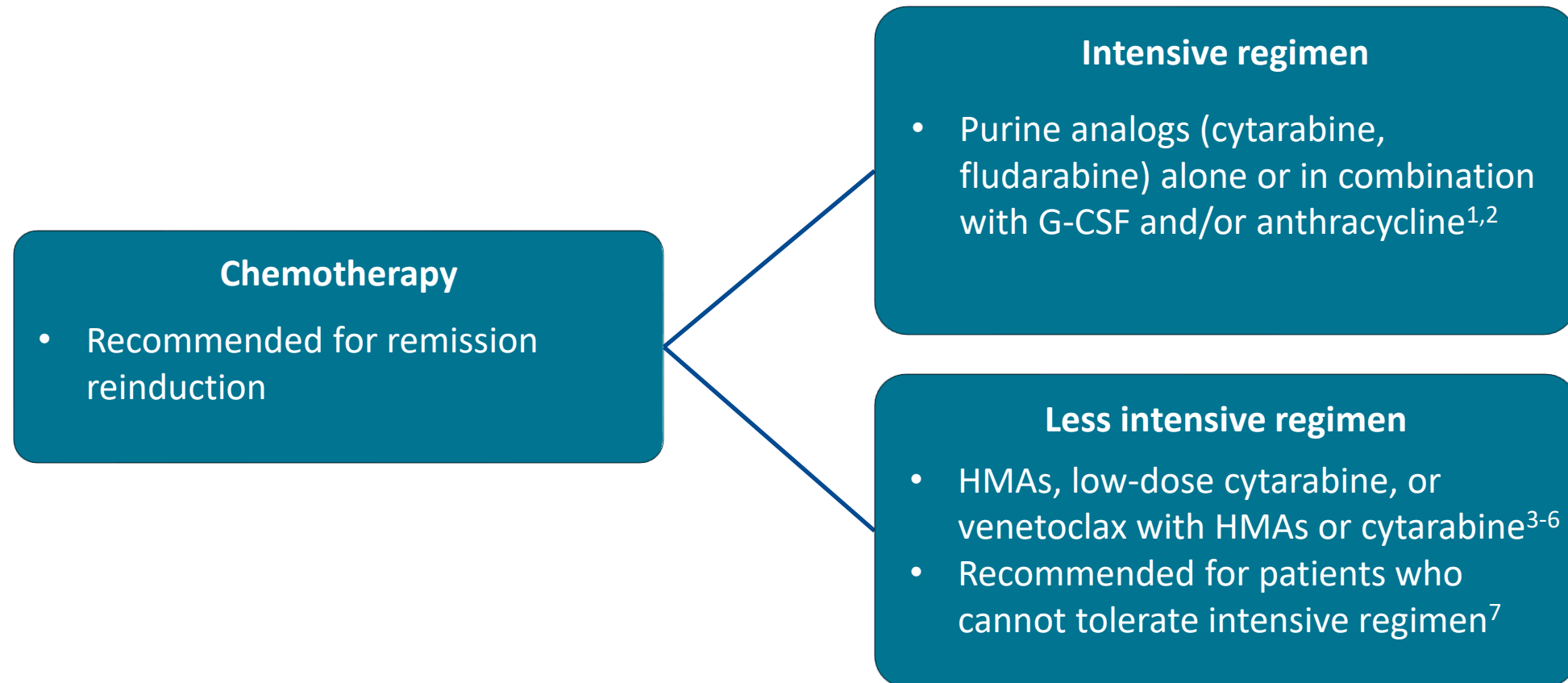
The Role of Shared Decision Making in Navigating the Complex Treatment Landscape of R/R AML

Current Treatment Landscape

Treating Relapsed or Refractory AML

Molecular profiling should be run if not originally done at diagnosis (or repeated to determine whether there has been clonal evolution)

Current Treatment Landscape of R/R AML: Chemotherapy



Abbreviations: AML, acute myeloid leukemia; G-CSF, granulocyte-colony stimulating factor; HMAs, hypomethylating agents; R/R, relapsed or refractory.

1. Robak, T, et al. *Leuk Lymphoma*. 2000;39(1-2):121-129. 2. Fridle C, et al. *Leuk Lymphoma*. 2017;58(5):1068-1075. 3. Al-Ali H.K, et al. *Leuk Lymphoma*. 2012;53(1):110-117. 4. Jensen, M.K, et al. *Eur J Haematol*. 1994;52(4):236-239. 5. Di Nardo C.D, et al. *Am J Hematol*. 2018;93(3):401-407. 6. Aldoss I, et al. *Haematologica*. 2018;103(9):e404-e407. 7. Heuser M, et al. *Ann Oncol*. 2020;31(6):697-712

Current Treatment Landscape of R/R AML: Targeted Therapy

Agent	Target(s)	Mechanism of Action	Notable Trial	Remission rates in R/R AML
Gilteritinib	<i>FLT3</i> -ITD <i>FLT3</i> -TKD	FLT3 inhibitor (mutant <i>FLT3</i> -ITD and <i>FLT3</i> -TKD)	NCT02421939 (ADMIRAL) ¹	34% (CR + CRh)
Quizartinib*	<i>FLT3</i> -ITD	FLT3 inhibitor	NCT00989261 ²	56% (CR+CRp+Cri)
Sorafenib + HMA [†]	<i>FLT3</i> -ITD	Multikinase inhibitor (including VEGFR, PDGFR and RAF kinases)	NCT01254890 ³	46% (CR+Cri+CRh)
Ivosidenib	<i>IDH1</i>	IDH1 inhibitor	NCT02074839 ⁴	21.6% (CR)
Olutasidenib	<i>IDH1</i>	IDH1 inhibitor	NCT02719574 ⁵	35% (CR+CRh)
Enasidenib	<i>IDH2</i>	IDH2 inhibitor	NCT01915498 ⁶	19.3% (CR)
Gemtuzumab ozogamicin	CD33+	Anti-CD33 antibody-drug conjugate	Taksin et al 2007 ⁷	26% (CR)

*Only approved for newly diagnosed *FLT3*-mutation positive AML. [†]Not approved but recommended for *FLT3*-mutation positive AML.

Abbreviation: AML, acute myeloid leukemia; CR, complete remission; CRp, complete remission with incomplete platelet recovery; CRh, complete remission with partial hematologic recovery; Cri, complete remission with incomplete hematologic recovery *FLT3*-ITD, fms-like tyrosine kinase 3-internal tandem duplication; *FLT3*-TKD, fms-like tyrosine kinase 3-tyrosine kinase domain; HMAs, hypomethylating agents; *IDH1*, isocitrate dehydrogenase-1; *IDH2*, isocitrate dehydrogenase-2; R/R, relapsed or refractory.

1. Perl A.E, et al. *Blood*. 2022; 139(23):3366-3375. 2. Cortes J, et al. *Lancet Oncol*. 2018;19(7):889-903. 3. Ravandi F, et al. *Blood*. 2013;121(23):4655-4662. 4. DiNardo C.D, et al. *N Engl J Med*. 2018;378(25):2386-98. 5. Botton S, et al. *Blood adv*. 2022;7(13):3117-3127. 6. Stein E.M, et al. *Blood*. 2017;130(6):722-731. 7. Taksin A.L, et al. *Leukemia*. 2007 Jan;21(1):66-71.

Current Treatment Landscape of R/R AML: Clinical Trials

Clinical trial enrollment may be appropriate for relapsed or refractory patients, especially those with targetable mutations and those who are ineligible for standard chemotherapy^{1,2}

Current Treatment Landscape of R/R AML: Select Ongoing* Clinical Trials

Agent	Actionable Alteration	Mechanism of Action	Trial	Intervention
Gilteritinib	<i>FLT3</i> mutation	FLT3 inhibitor (mutant <i>FLT3</i> -ITD and <i>FLT3</i> -TKD)	NCT05010122 Phase I/II ¹	Gilteritinib, venetoclax, and ASTX727 (decitabine + cedazuridine)
Quizartinib	<i>FLT3</i> -ITD mutation	FLT3 inhibitor	QuANTUM-R (NCT02039726) Phase III ²	Quizartinib monotherapy vs salvage chemotherapy
Revumenib	<i>KMT2A</i> rearrangement <i>NPM1</i> mutation	Menin inhibitor	AUGMENT-101 (NCT04065399) Phase I/II ³	Revumenib (Phase II)
Ziftomenib	<i>NPM1</i> mutation	Menin inhibitor	NCT04067336 Phase I/II ⁴	Ziftomenib

*As of June 2024.

Abbreviations: AML, acute myeloid leukemia; FLT3-ITD, fms-like tyrosine kinase 3-internal tandem duplication; FLT3-TKD, fms-like tyrosince kinase 3-tyrosine kinase domain; NPM1, nucleophosmin ; KMT2A, Lysine Methyltransferase 2A; R/R, relapsed or refractory.

1. ClinicalTrials.gov. Accessed 05/18/24 at <https://classic.clinicaltrials.gov/ct2/show/NCT05010122>. 2. ClinicalTrials.gov. Accessed 06/05/24 at <https://classic.clinicaltrials.gov/ct2/show/NCT02039726>. 3. ClinicalTrials.gov. Accessed 06/06/24 at <https://classic.clinicaltrials.gov/ct2/show/NCT04065399>. 4. ClinicalTrials.gov. Accessed 06/05/24 at <https://clinicaltrials.gov/study/NCT04067336>.

Current Treatment Landscape of R/R AML: Select Ongoing* Clinical Trials

	Mechanism of Action	Trial	Intervention
Quizartinib	FLT3 inhibitor (treats <i>FLT3</i> -ITD and <i>FLT3</i> -TKD)	NCT05010122 Phase I/II ¹	Gilteritinib, venetoclax, and ASTX727 (decitabine + cedazuridine)
Revumenib	FLT3 inhibitor	QuANTUM-R (NCT02039726) Phase III ²	Quizartinib monotherapy vs salvage chemotherapy
Ziftomenib	<i>KMT2A</i> rearrangement, <i>NPM-1</i> mutant	AUGMENT-101 (NCT04065399) Phase I/II ³	Revumenib (Phase II)
		NCT04067336 Phase I/II ⁴	Ziftomenib

FDA granted breakthrough designation to **revumenib** in R/R *KMT2A*-rearranged AML⁵

FDA granted breakthrough designation to **ziftomenib** for heavily pretreated patients with R/R *NPM1*-mutant AML⁶

*As of June 2024.

Abbreviations: AML, acute myeloid leukemia; FLT3-ITD, fms-like tyrosine kinase 3-internal tandem duplication; FLT3-TKD, fms-like tyrosine kinase 3-tyrosine kinase domain; NPM1, nucleophosmin; KMT2A, Lysine Methyltransferase 2A; R/R, relapsed or refractory.

1. ClinicalTrials.gov. Accessed 05/18/24 at <https://classic.clinicaltrials.gov/ct2/show/NCT05010122>. 2. ClinicalTrials.gov. Accessed 06/05/24 at <https://classic.clinicaltrials.gov/ct2/show/NCT02039726> 3. ClinicalTrials.gov. Accessed 06/06/24 at <https://classic.clinicaltrials.gov/ct2/show/NCT04065399> 4. ClinicalTrials.gov. Accessed 06/05/24 at <https://clinicaltrials.gov/study/NCT04067336> 5. PR Newswire. Accessed June 6, 2024 at <https://www.prnewswire.com/news-releases/syndax-announces-us-fda-breakthrough-therapy-designation-granted-for-revumenib-for-the-treatment-of-adult-and-pediatric-patients-with-relapsed-or-refractory-kmt2a--rearranged-mlr-acute-leukemia-301694253.html> 6. Globenewswire. Accessed June 6, 2024 at <https://www.globenewswire.com/news-release/2024/05/02/2874668/35186/en/Kura-Oncology-Reports-First-Quarter-2024-Financial-Results.html>.

Current Treatment Landscape of R/R AML: Allogeneic Hematopoietic Stem Cell Transplantation (alloHCT)

- Performed for a patient who is fit and hasn't received a transplant in the past¹
- Only potentially curative option for refractory and relapse AML^{2,3}
- Plausible consolidation therapy after reaching complete remission³

Factors Influencing Treatment Selection in R/R AML



Disease and treatment-related

- Risk-stratification
- Mutations profile
- Previous induction regimen
- Duration of previous remission
- Treatment toxicity/tolerability



Patient-related

- Age
- Fitness level
- Comorbidities
- Quality of life
- Social support
- Patient preferences

The Role of Shared Decision Making in Navigating the Complex Treatment Landscape of R/R AML

Shared Decision Making in R/R AML

Shared Decision Making (SDM)^{1,2}

Two-way communication approach in which patients and clinicians collaborate to make an informed treatment decision

SDM applies to preference-sensitive medical conditions, such as AML, in which more than one treatment option is available and the clinical evidence does not support one treatment option over another.

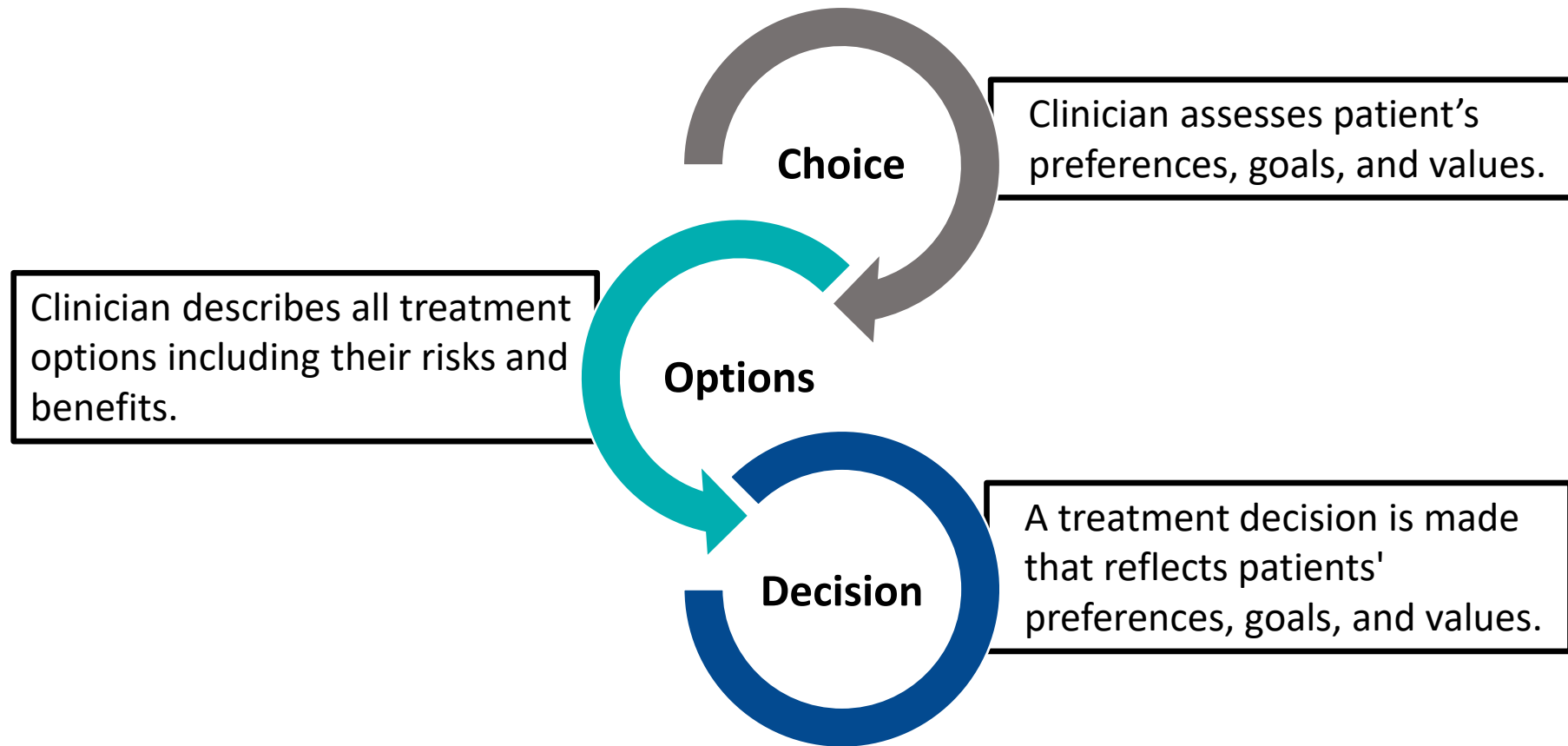
Treatment decisions should align with patients' values, goals, preferences, and concerns

Abbreviations: AML, acute myeloid leukemia; SDM, shared decision making

1. National Quality Forum. Shared Decision Making: A Standard of Care for All Patients. Accessed 05/12/2024 at

https://www.qualityforum.org/Publications/2017/10/NQP_Shared_Decision_Making_Action_Brief.aspx 2. LeBlanc T.W, *Seminars in Oncology Nursing*. 2019;35(6):150958

Choice Options Decision (COD) Framework^{1,2}



Abbreviations: SDM, shared decision making

1. Elwyn G, et al. *J Gen Intern Med*. 2012;27(10):1361-1367. 2 .LeBlanc T.W, *Seminars in Oncology Nursing*. 2019;35(6):150958

8 Domains of Decision Quality in SDM

Reasonable Options

Clinician determines what are reasonable treatment options. The shared decision-making process then focuses on this menu.

Accessibility

Insurance coverage status and out of pocket expenses, as applicable, are understood and factored into the decision.

Decision Style Preference

Style preference is articulated and respected by patient and clinician.

Knowledge

Patient and clinician have a shared working knowledge of the most important information involved in the decision.

Risk/Burden Tolerance

Risk tolerance is defined, discussed, and aligned with discussion of wellness options.

Activation, Engagement, Self-Efficacy

Decision is realistically aligned with and encourages activation, self-efficacy, and engagement.

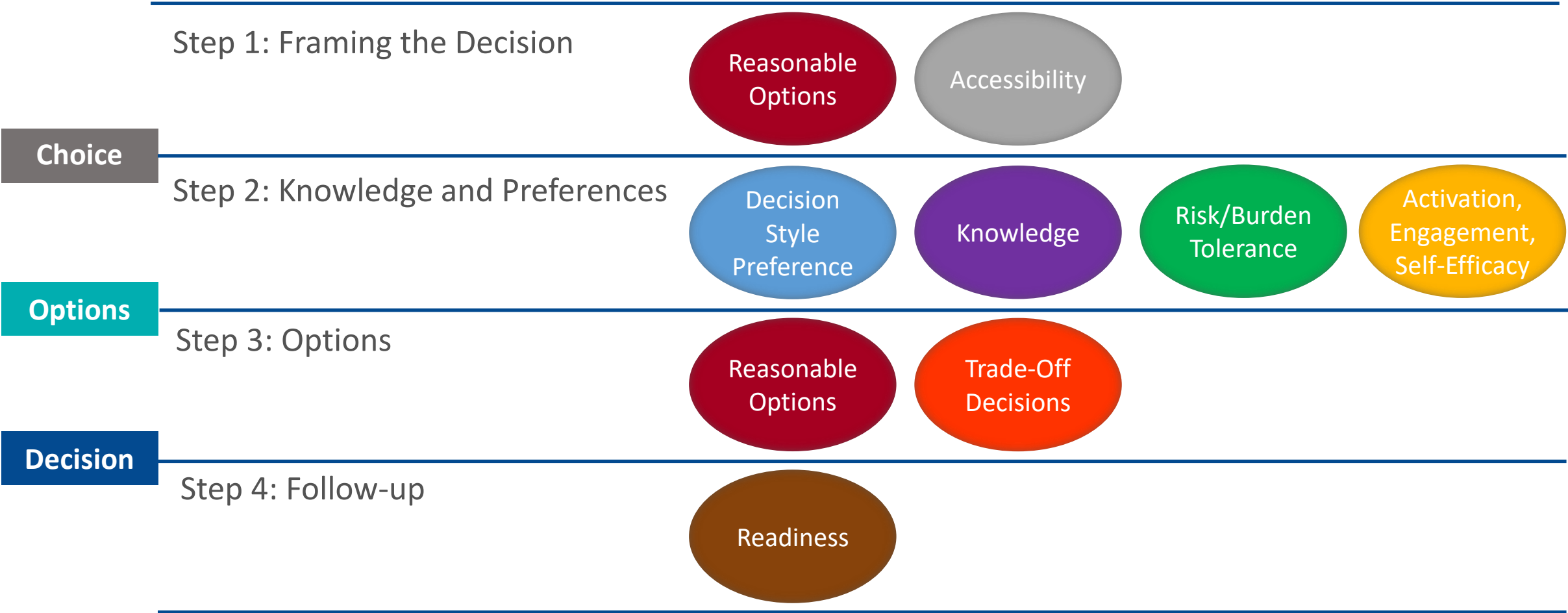
Trade-Off Decisions

Trade-offs are made explicit, are articulated, and are understood by patient and clinician.

Readiness

Patient and clinician feel confident and comfortable in making the decision.

4-Step Practical Approach to 8 Domains¹⁻³

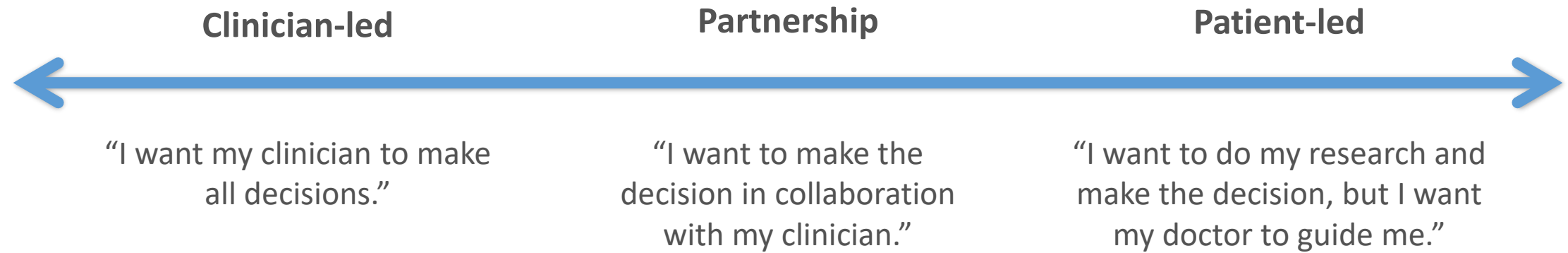


Reasonable options



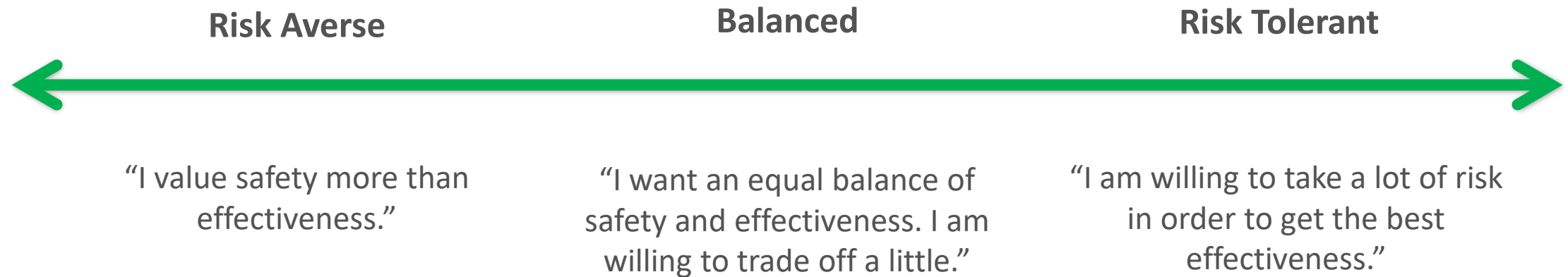
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Decision Style Preferences



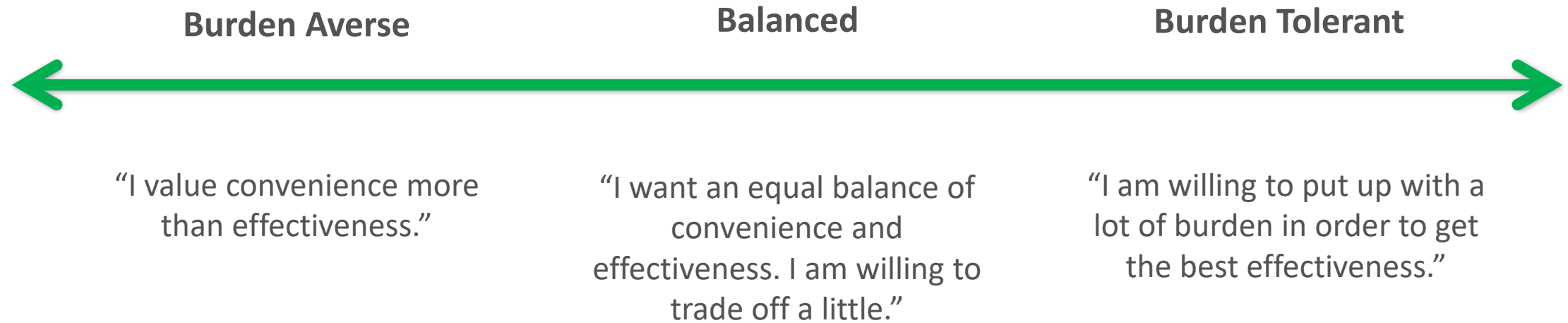
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Risk Tolerance



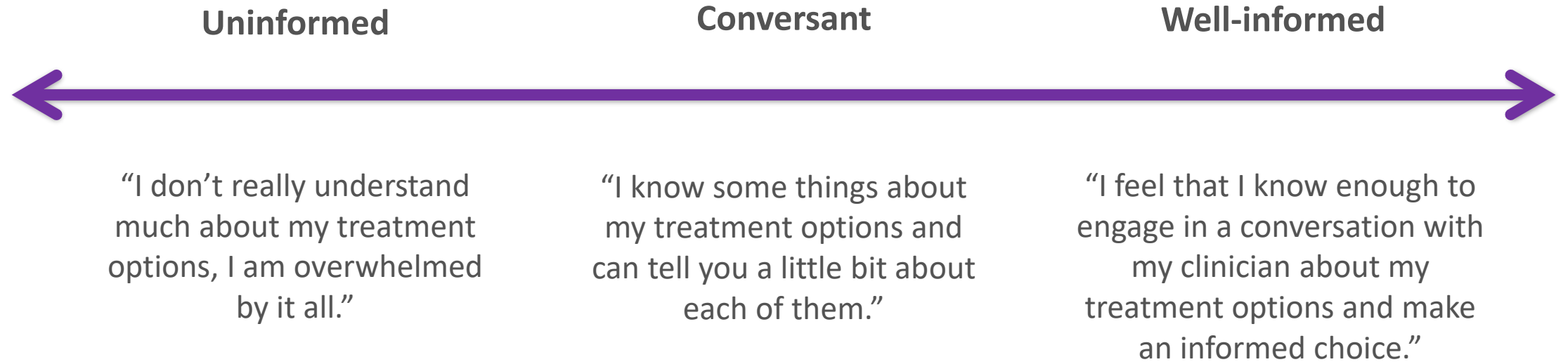
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Burden Tolerance



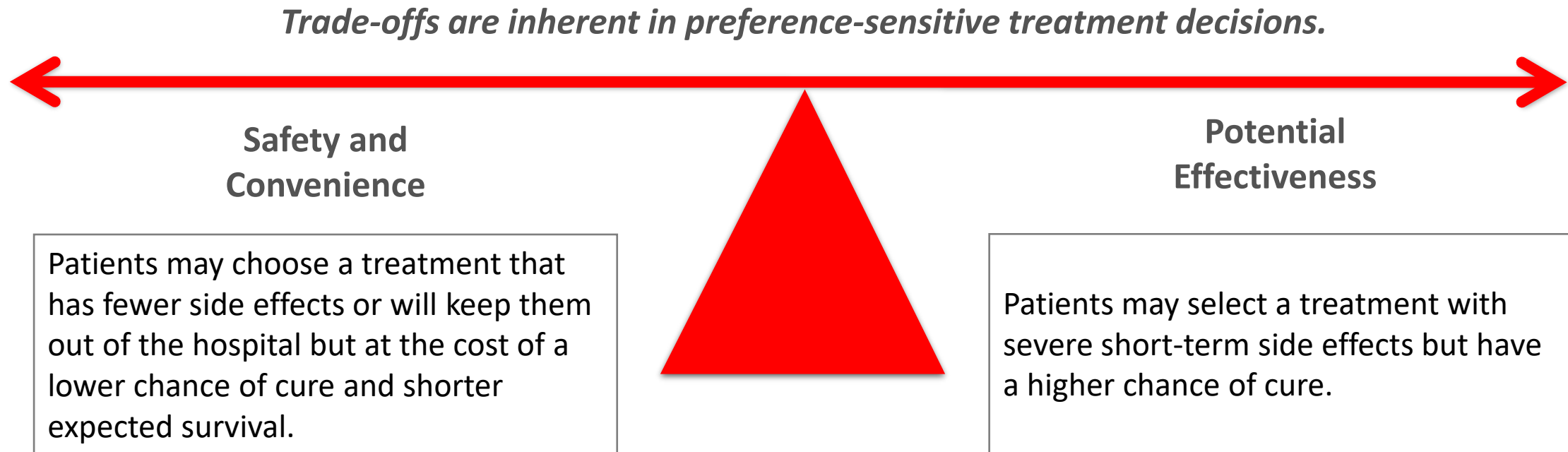
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Knowledge



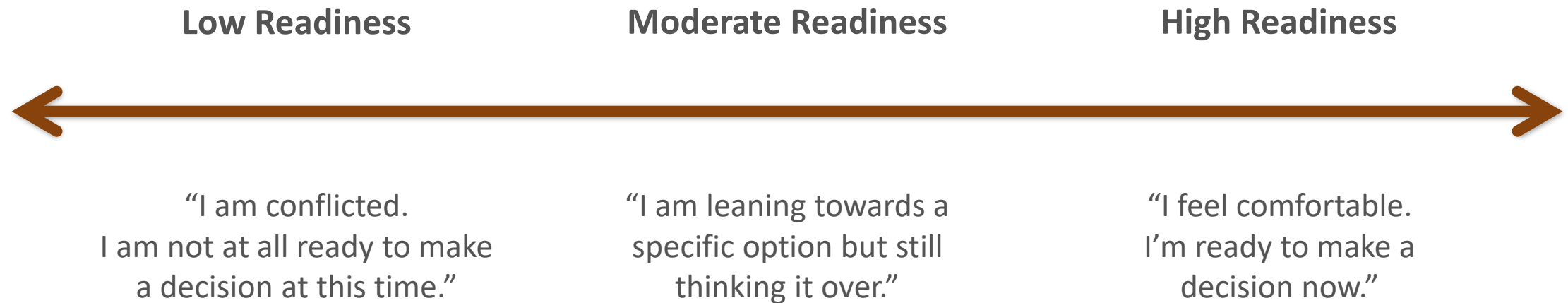
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Trade-Off Decisions^{1,2}



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Readiness



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Overcoming Barriers to the Implementation of SDM in Clinical Practice

Barriers	Suggested solutions
Lack of leadership support and/or buy-in	• Provide leadership with data to show that SDM improve patient health outcomes
Skepticism about the value and importance of SDM	• Focus on the impact that SDM and engaged patients can have on financial goals • Engage patients and advocates to share stories about the impact of SDM on patients and families
Competing priorities, “initiative fatigue” and burnouts	• Initially implement at small-scale, and then use its success to gain support for large-scale implementation
Patient are unclear about their role in the SDM process	• Create clear message about SDM, including what patients can expect • Explain them how to actively engage in discussion by asking questions • Understand their preferences
Low health literacy or numeracy of patients and their caregivers Non-native speakers of English	• Use plain language and visual-aids to describe diagnosis and treatment options. • Use teach-back technique

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Communication Strategies

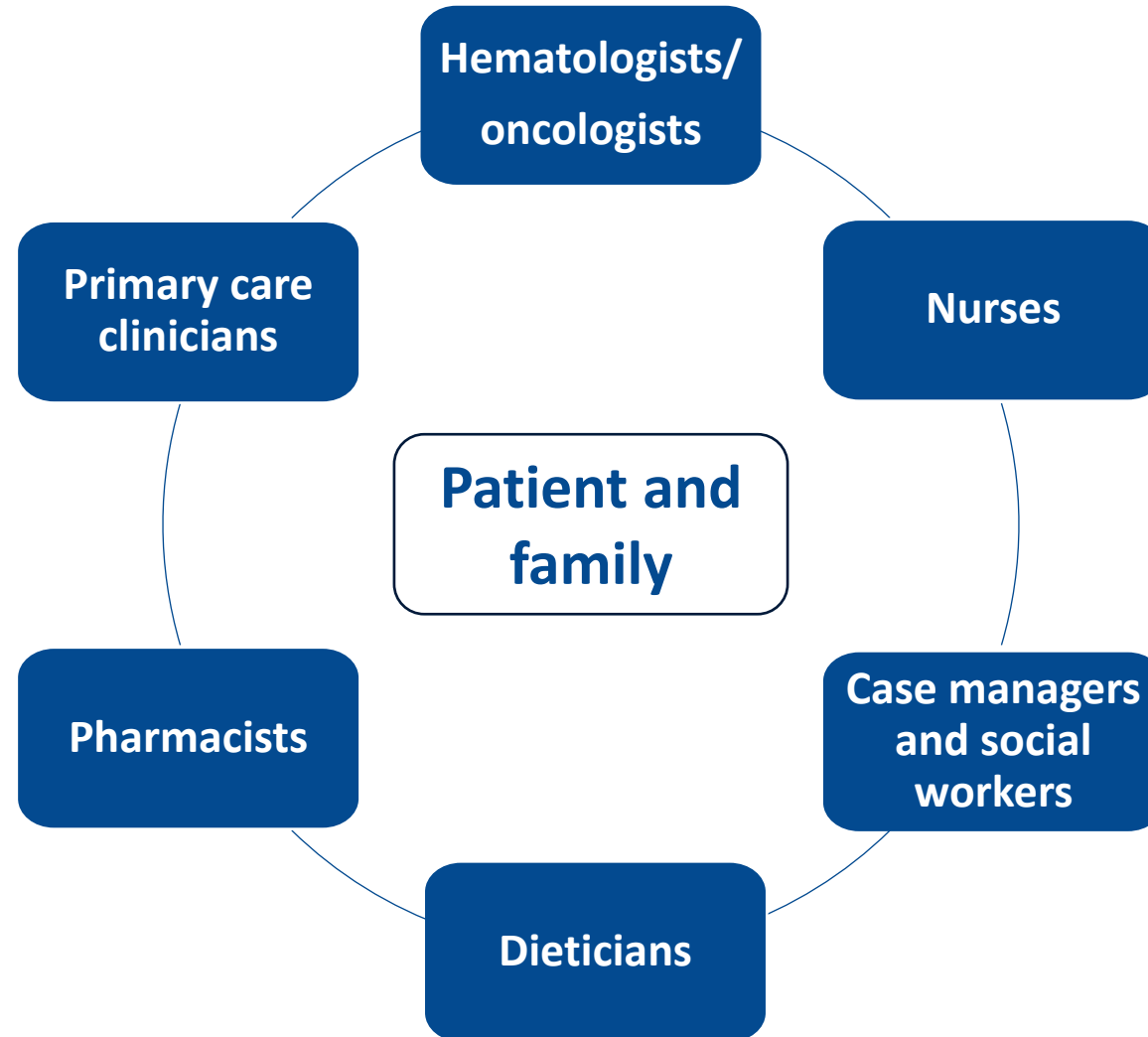
Communication Strategies

Patients prefer a patient-centered communication approach in the patient-clinician relationship

Features of Patient-Centered Communication

-  Listen actively
-  Take time to speak with patients
-  Use a warm tone of voice
-  Sit next to the patient and maintain eye contact
-  Use easy-to-understand language with minimum jargon
-  Apply teach-back methodology to ensure that the patient understands the information
-  Use visual aids to explain complex treatment options
-  Pay attention to a patient's emotions
-  Empathize with the patient
-  Acknowledge their worries and concerns

Multidisciplinary team in SDM¹⁻⁴



Abbreviations: SDM, Shared decision making

1. Rudell E, et al. Poster P6-05-15. Presented at: 2022 SABCS®; December 6-10, 2022; San Antonio, TX. 2. LeBlanc T.W, *Seminars in Oncology Nursing*. 2019;35(6):150958. 3. Morikawa M, et al. *Cancer Control*. 2022; 29:1-9. 4. Benton C, et al. *Front. Oncol*. 2022;12:1060912.

Patient-Related Factors to Consider During Treatment Discussions



Lifestyle of the patient



Family and social support system



Dependency on a caregiver



Transportation situation



Ability to keep up with follow-up appointments

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Summary

Summary

- As part of the dynamic nature of AML, the appearance and/or disappearance of mutations over the progression of the disease necessitates genomic re-evaluation in relapsed or refractory disease
- Mutational analysis helps clinicians with risk stratification and the prediction of relapse risks, remission, and overall survival outcomes, and facilitates the selection of appropriate targeted therapies
- The SDM process should play a significant role in AML treatment decisions
- SDM is a two-way communication approach in which a patient and clinician collaborate to make an informed treatment decision that aligns with the patient's preferences, goals, and values



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