

Representing Clinically Relevant Medication Knowledge

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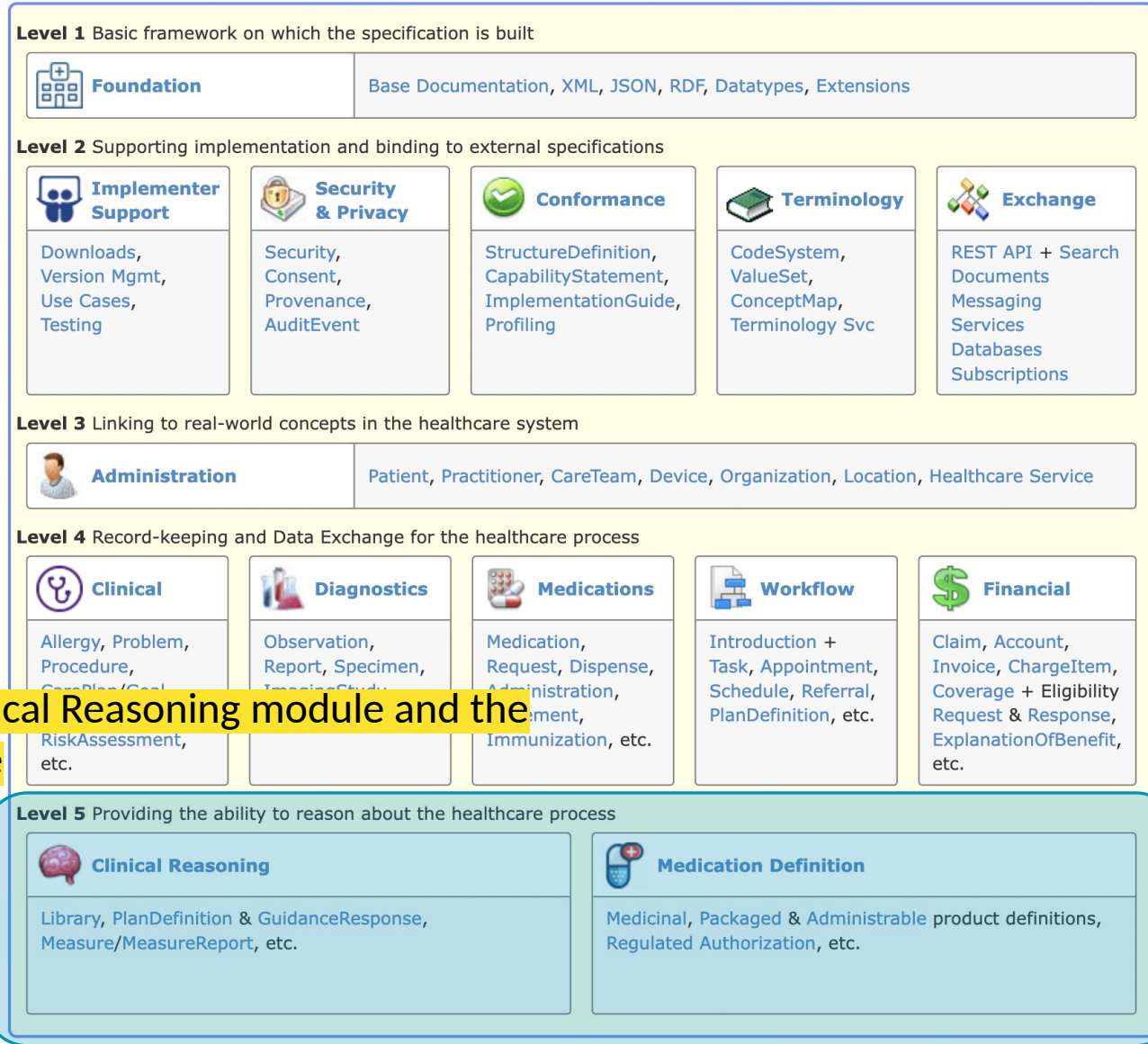
Who am I?

- Joonatan Vuorinen
- Systems Architect
- Duodecim Publishing Company Ltd.
- Working on...
 - Authoring and executing clinical reasoning
 - Clinical practice guidelines
 - Evidence based medicine
 - *Medication knowledge bases*



What is “Clinically Relevant Medication Knowledge”?

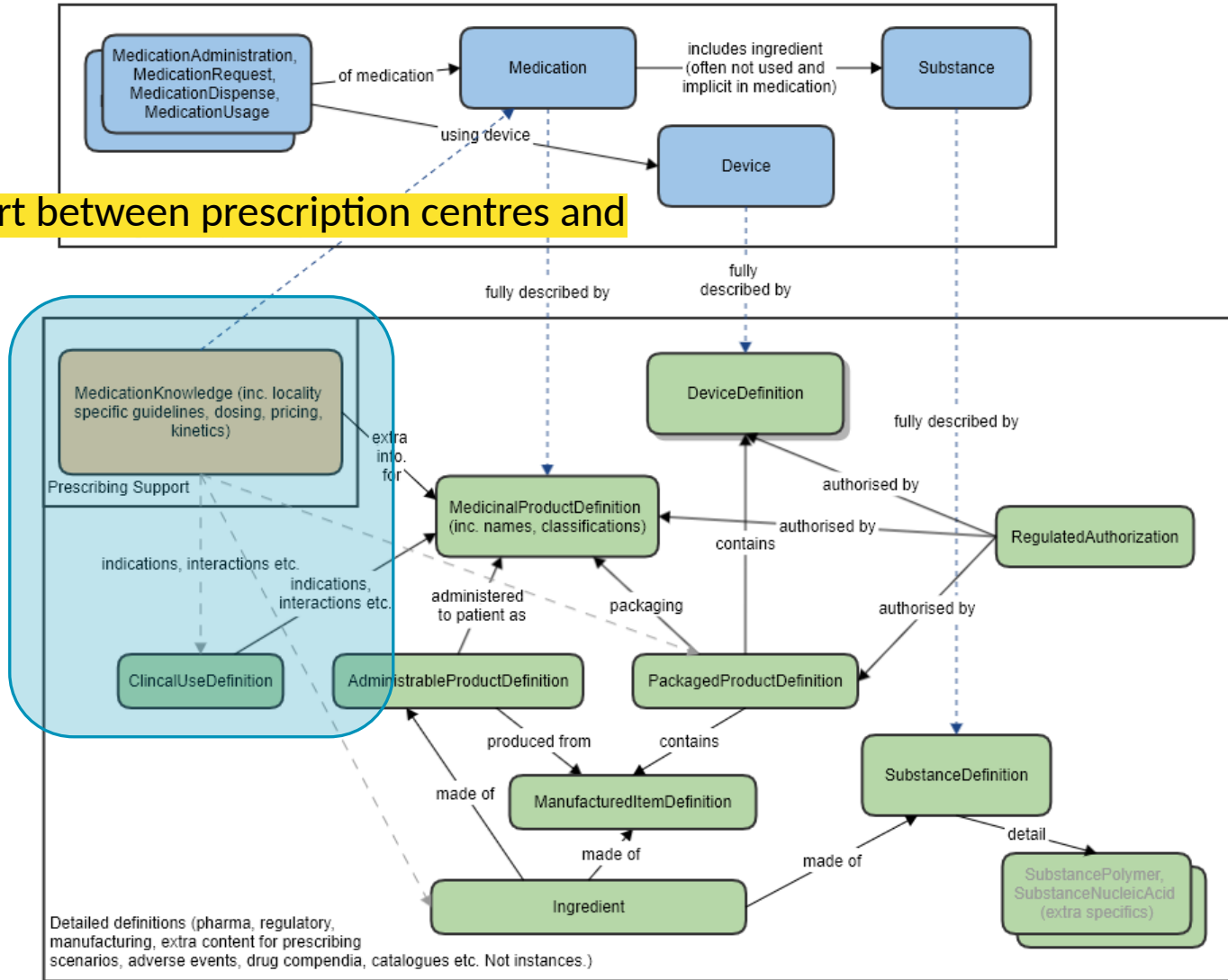
Artifact Category	Description	Resources
Knowledge Artifacts	Representing decision support rules, quality measures, logic libraries, and activity definitions	ActivityDefinition Library Measure PlanDefinition Questionnaire
Terminology Artifacts	Code systems, value sets, naming systems, and concept maps	ValueSet CodeSystem ConceptMap NamingSystem
Conformance Artifacts	Profiles, extensions, structure maps, and artifacts related to defining and testing conformance	GraphDefinition ImplementationGuide StructureDefinition StructureMap
CRMI Domain Artifacts		
Domain Artifacts	Medications, substances, groups, and other domain-related artifacts	CareTeam (<i>profiled</i>) Group (non-canonical artifact) Location (<i>profiled</i>) Medication (non-canonical artifact) MedicationKnowledge (non-canonical artifact) Practitioner (<i>profiled</i>) PractitionerRole (<i>profiled</i>) Organization (<i>profiled</i>) Substance (non-canonical artifact)
Evidence-based Medicine (EBM) Artifacts (Roadmap)	Artifacts related to supporting evidence-based medicine	Evidence EvidenceVariable



At the intersection of the Clinical Reasoning module and the Medication Definition module

Enabling prescribing support between prescription centres and medicines agencies

Knowledge bases e.g., Meds75+



Prescription centres e.g., Kela

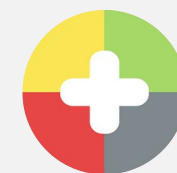
Medicines agencies e.g., EMA, Fimea

What is “Clinically Relevant Medication Knowledge”?

- CRMI Domain Artifacts
- At the intersection of the Clinical Reasoning module and the Medication Definition module
- Enabling prescribing support between prescription centres and medicines agencies
- **In short; MedicationKnowledge & ClinicalUseDefinition**

Example: Representing Meds75+

- “The purpose of the Meds75+ is **to support the clinical decision-making on the pharmacotherapy of adults over 75 years of age** and to improve medication safety in primary health care.”
- Open data maintained by the Finnish Medicines Agency (Fimea)
- **Classifies drug substances** to one of four classes
 - **A** (green): *Suitable* for older adults
 - **B** (grey): Current evidence on or experience with use in older adults is *inconclusive* or the medicine is *insufficiently effective* in the older adults
 - **C** (yellow): Suitable for older adults, with *specific precautions*
 - **D** (red): *Avoid use* in older adults



Meds75+

```

<Laakeaine ainetunnus="1452">
  <Ainenimi>Diclofenac sodium</Ainenimi>
  <ATC-koodi>M01AB55</ATC-koodi>
  <ATC-selite>diklofenaakki, yhdistelmävalmisteet</ATC-selite>
  <Luokka>C</Luokka>
  <KommenttiFI>Soveltuu varauksin iäkkäille. Vain lyhytaikaiseen käyttöön. Älä käytä vaikeassa
  munuaisten vajaatoiminnassa. Lisää turvotuksia, pahentaa munuaisten ja sydämen
  vajaatoimintaa sekä aiheuttaa sydän- ja verisuonitapahtumia. Lisää verenvuodon riskiä,
  erityisesti ruuansulatuskanavassa. Huomioi yhteisvaikutukset, etenkin verenvuotoa lisäävien
  lääkkeiden kanssa. (päivitetty 13.12.2021)</KommenttiFI>
  <KommenttiSV>Lämpar sig med förbehåll för äldre personer. Endast för kortvarigt bruk. Använd
  inte vid svår njursvikt. Ökar svullnad, förvärrar njursvikt och hjärtsvikt och orsakar
  hjärt- och kärlhändelser. Ökar risken för blödningar, särskilt i magtarmkanalen. Beakta
  interaktioner, särskilt med preparate som ökar risken för blödningar. (uppdaterad
  13.12.2021)</KommenttiSV>
  <KommenttiEN>Suitable for older adults, with specific precautions. For short-term use only. Do
  not use in severe renal impairment. Increases swelling, worsens renal and cardiac failure
  and causes cardiovascular events. Increases risk of bleeding, especially in gastrointestinal
  tract. Consider potential interactions, especially with preparations that increase risk of
  bleeding. (updated 13.12.2021)</KommenttiEN>
  <LuokitteluPvm>2021-12-13</LuokitteluPvm>
  <Pakkauslista>
    <Pakkaustunnus id="7798" Nimi="Arthrotec" VNR="154591" />
    <Pakkaustunnus id="7799" Nimi="Arthrotec" VNR="154708" />
    <Pakkaustunnus id="8920" Nimi="Arthrotec Forte" VNR="431759" />
    <Pakkaustunnus id="8921" Nimi="Arthrotec Forte" VNR="431783" />
  </Pakkauslista>
</Laakeaine>
  
```

Specific ingredient
Active substances
Classification

Recommendation

Date of classification

Products

Identifying products and active substances (1/3)

- **Products** are identified by a *Nordic Article Number (Vnr)*
 - E.g., 154591 "Arthrotec"
- **Active substances** are identified by an *Anatomical Therapeutic Chemical (ATC)* classification code
 - E.g., M01AB55 "diclofenac, combinations"
- **Specific ingredients** are identified by a *substance identifier* managed by the Finnish Medicines Agency (Fimea)
 - E.g., 1452 "Diclofenac sodium"

Identifying products and active substances (2/3)

```

Instance: Meds75-M01AB55-1452
InstanceOf: MedicationKnowledge
* insert Vnr(154591, [{"Arthrotec"}])
* insert Vnr(154708, [{"Arthrotec"}])
* insert Vnr(431759, [{"Arthrotec Forte"}])
* insert Vnr(431783, [{"Arthrotec Forte"}])
* code = $ATC#M01AB55 "diclofenac, combinations"
* insert Classification(C-M01AB55-1452)
* insert Ingredient(1452, [{"Diclofenac sodium"}])
  
```

A generated intermediary FHIR Shorthand (FSH) instance

```

{
  "resourceType": "MedicationKnowledge",
  "id": "Meds75-M01AB55-1452",
  "identifier": [...],
  "code": {...},
  "medicineClassification": [...],
  "definitional": {
    "ingredient": [...],
  }
}
  
```

Identifying products and active substances (3/3)

- **Products change quicker** than substances (e.g., biweekly vs quarterly)
 - It may be worthwhile to separate the mechanism for identifying products in each jurisdiction from the authored MedicationKnowledge
- **Using ATC** as the coding for active substances **introduces the need for a separate substance identifier** for dealing with combination drugs
 - This could likely be avoided by using a code system supporting more complex hierarchies, such as SNOMED CT or RxNorm
- **EMA SPOR Product Management Services (PMS) and Substance Management Services (SMS) may centralize these concerns in the EU**

An example classification and recommendation

- Classification:
 - **C** (yellow): *"Suitable for older adults, with specific precautions"*
- Recommendation:
 - For short-term use only.
 - Do not use in severe renal impairment.
 - Increases swelling, worsens renal and cardiac failure and causes cardiovascular events.
 - Increases risk of bleeding, especially in gastrointestinal tract.
 - Consider potential interactions, especially with preparations that increase risk of bleeding.

Representing the classification as a CodeSystem (1/2)

- The classification can be represented as hierarchical a CodeSystem
 - The **first level** contains the **classification** (i.e., A,B,C,D)
 - The **second level** contains the **recommendation** for each substance

```
* #C "Suitable for older adults, with specific precautions"
```

```
* #C-M01AB55-1452 "Suitable for older adults, with specific precautions. For short-term use only. Do not use in severe renal impairment. Increases swelling, worsens renal and cardiac failure and causes cardiovascular events. Increases risk of bleeding, especially in gastrointestinal tract. Consider potential interactions, especially with preparations that increase risk of bleeding. (updated 13.12.2021)"
```

Representing the classification as a CodeSystem (2/2)

- Pros:
 - **A workable knowledge base** with just MedicationKnowledge and CodeSystem
 - Can be **entirely machine-generated** without changing the source data
 - Representable with **CRMI profiles**
 - **Maps well to the search parameters** on MedicationKnowledge
 - **Easy localization** through CodeSystem designations
- Cons:
 - **Including recommendations in the CodeSystem misses an opportunity** of modelling them as ClinicalUseDefinition resources, bloating the CodeSystem

Decomposing the recommendation (1/2)

```
// "For short-term use only."
* clinicalUseIssue[+] = Reference(diclofenac-warning-for-short-term-use-only)
// "Do not use in severe renal impairment."
* clinicalUseIssue[+] = Reference(diclofenac-contraindication-acute-renal-failure)
// "Increases swelling, worsens renal and cardiac failure and causes cardiovascular events."
* clinicalUseIssue[+] = Reference(diclofenac-undesirable-effect-swelling)
* clinicalUseIssue[+] = Reference(diclofenac-undesirable-effect-kidney-symptom)
* clinicalUseIssue[+] = Reference(diclofenac-undesirable-effect-heart-failure)
* clinicalUseIssue[+] = Reference(diclofenac-undesirable-effect-cardiovascular-disease)
// "Increases risk of bleeding, especially in gastrointestinal tract."
* clinicalUseIssue[+] = Reference(diclofenac-undesirable-effect-rectal-bleeding)
// "Consider potential interactions, especially with preparations that increase risk of bleeding."
* clinicalUseIssue[+] = Reference(diclofenac-warning-consider-interactions-risk-of-bleeding)
```

```
Instance: diclofenac-contraindication-acute-renal-failure
InstanceOf: ClinicalUseDefinition
* type = #contraindication
* insert DiclofenacSubstancesAsSubjects
* contraindication.diseaseSymptomProcedure.concept
  * coding[+] = $ICD10#N17 "Insufficiencia renalis acuta"
  * coding[+] = $SCT#14669001 "Acute kidney injury"
```

```
Instance: diclofenac-undesirable-effect-swelling
InstanceOf: ClinicalUseDefinition
* type = #undesirable-effect
* insert DiclofenacSubstancesAsSubjects
* undesirableEffect.classification
  * coding[+] = $ICPC#A08 "Swelling"
  * coding[+] = $SCT#65124004 "Swelling"
```

Decomposing the recommendation (2/2)

- Pros:
 - Enables a knowledge base with **coded interactions, contraindications, etc.**
 - **The #warning type can be used as a placeholder** when moving towards more structured ClinicalUseDefinition resources
 - Potential for **reuse across MedicationKnowledge resources**
- Cons:
 - **Modeling takes a lot of effort**, especially for terminologies
 - ClinicalUseDefinition currently uses a Reference as a subject instead of a code, meaning that **you'll need a substance register** as well
 - ClinicalUseDefinition is **not a part of CRMI** (yet?)

Prescribing support through CDS Hooks

- A knowledge base can be wrapped with a CDS Hooks service to provide prescribing support on the **order-select** and **order-sign** hooks
 - ...given the prescribed medications and the authored MedicationKnowledge are mapped

MedicationRequest identified by Vnr and/or ATC →

(Metformin hydrochloride) C: Suitable for older adults, with specific precautions. ^

Reduce the dose already in mild renal impairment. Do not use in severe renal impairment or tissue hypoxia. May reduce the absorption of vitamin B12. Consider risk of lactic acidosis. The drug should be paused during fever, gastroenteritis or dehydration, and before surgery or imaging with a contrast agent. (updated 25.10.2021)

Source

 [Duodecim Clinical Decision Support - Meds75+](#)

Takeaways

- Third-party medication knowledge bases remain necessary
 - For example, EMA SPOR PMS contains structured indications, but is missing other structured clinical particulars, like interactions and contraindications
- CRMI provides a good base for authoring and sharing knowledge
- Mapping between the authored MedicationKnowledge and the prescribed medication in a sensible way is vital
 - This applies to products, substances, drug forms, and routes of administration
- Knowledge bases may be considered as simple search from a regulatory perspective, such as MDR in the EU (YMMV!)

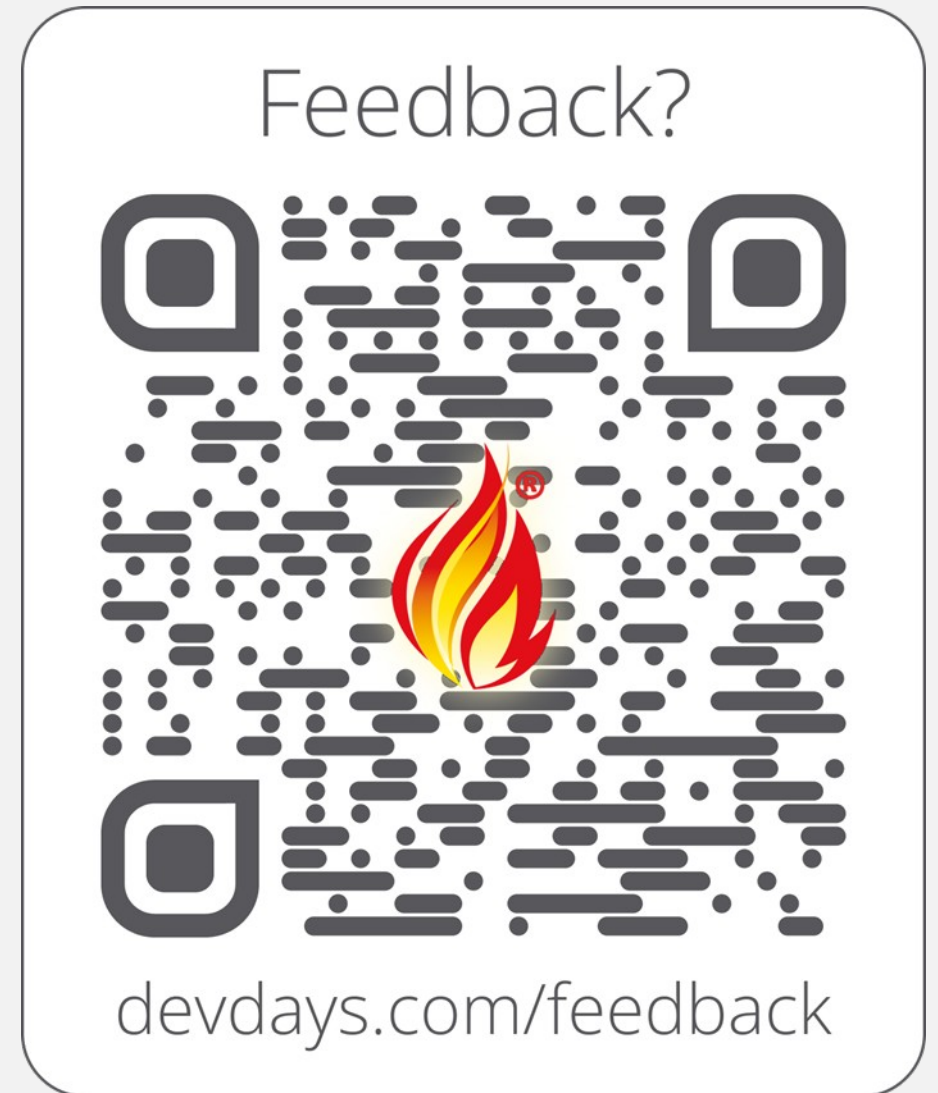
Contact

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Q&A

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